(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 27 March 2003 (27,03,2003)

PCT

(10) International Publication Number WO 03/024448 A2

- (51) International Patent Classification?: A61K 31/44, 31/506, 31/16, 31/472, 31/47, 31/428, 31/41, C07D 213/74, 401/12, 405/12, 213/82, C07C 237/20, C07D 215/38, 215/36, 239/42, 239/52, 217/04, 277/82, 277/42, 257/04, A61P 35/00
 - ζ,
- (21) International Application Number: PCT/US02/29017
- (22) International Filing Date:

12 September 2002 (12.09.2002)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/322,402 14 September 2001 (14.09.2001) US 60/391,728 26 June 2002 (26.06.2002) US

- (71) Applicant (for all designated States except US): METHYLGENE, INC. [CA/CA]; 7220 Frederick-Banting, St. Laurent, Quebec H4S 2A1 (CA).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DELORME, Daniel [CA/CA]; 793 Charbonneau, St-Lazare, Quebec J7T 2B2 (CA). WOO, Soon, Hyung [KR/US]; 1161 Nimitz Lane, Foster City, CA 94404 (US). VAISBURG, Arkadii [CA/CA]; 10 Riverwood Grove, Kirkland, Quebec H9J 2X2 (CA). MORADEL, Oscar [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). LEIT, Silvana [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). RAEPPEL, Stephane [FR/CA]; 5041 Laurin, Pierrefonds, Quebec H8Y 3R4 (CA). FRECHETTE, Sylvie [CA/CA]; 2380 Duff Court apt.#8,

Lachine, Quebec H8S 1G2 (CA). BOUCHAIN, Giliane [FR/CA]; 247 Glengary Avenue, Beaconsfield, Quebec H9W 5X9 (CA).

- (74) Agent: GREENFIELD, Michael, S.; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Suite 3200, Chicago, IL 60606 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

- of inventorship (Rule 4.17(iv)) for US only

Published:

 without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions.

INHIBITORS OF HISTONE DEACETYLASE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity. Summary of the Related Art

[0002] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0003] Csordas, *Biochem. J.*, **286**: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the α,ε-amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science*, **272**: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0004] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger et al., Proc. Natl. Acad. Sci. USA, 96: 4868-4873 (1999), teaches that HDACs is divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger et al. also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao et al., Genes & Dev., 14: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, FEBS, 478: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs.

[0005] Richon et al., Proc. Natl. Acad. Sci. USA, 95: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from Streptomyces hygroscopicus, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, Exper. Cell Res., 177: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G₁ and G₂ phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin et al., Nature, 401: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki et al., U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme et al., WO 01/38322 and PCT IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

[0006] The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger et al., Proc. Natl. Acad. Sci. USA, 96:4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger et al. also teaches that the human HDAC-1, HDAC-2, and HDAC-3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC-4, HDAC-5, and HDAC-6, which are members of the second class of HDACs. Kao et al., Gene & Development 14:55-66 (2000), discloses an additional member of this second class, called HDAC-7. More recently, Hu, E. et al. J. Bio. Chem. 275:15254-13264 (2000) discloses the newest member of the first class of histone deacetylases, HDAC-8. It has been unclear what roles these individual HDAC enzymes play.

[0007] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

BRIEF SUMMARY OF THE INVENTION

[0008] The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0009] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0010] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0011] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0012] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 is a graph showing the antitumor activity of compound **106** in an HCT 116 human colorectal tumor model.

[0014] Figures 2-11 show additional data for other compounds used in the *in vivo* experiment described in Assay Example 2.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0016] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0017] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ,-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6,

HDAC-7, and HDAC-8. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0018] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity. "Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0019] Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0020] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (e.g. CH₃-CH₂-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., -CH₂-CH₂-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as (A)_a-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure.

[0021] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A " C_0 " hydrocarbyl is used to refer to a covalent bond. Thus, " C_0 - C_3 -hydrocarbyl" includes a covalent bond, methyl, ethyl, propyl, and cyclopropyl.

[0022] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C₀" alkyl (as in "C₀-C₃-alkyl") is a covalent bond (like "C₀" hydrocarbyl).

[0023] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0024] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0025] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butynylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0026] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0027] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteratom selected from the group consisting of O, S, and N.

[0028] An "aryl" group is a C_6 - C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6 - C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is $(C_1$ - C_6)alk $(C_6$ - C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0029] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. The heterocyclic group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocyles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0030] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroalkyl groups comprise a C_1 - C_6 alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular 0 and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular 0 and/or S atoms.

[0031] An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0032] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aHcarbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroguinolinyl, 2H.6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1Hindazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyrazyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienoxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0033] As employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular - CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

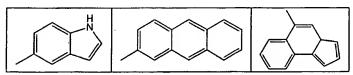
- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,
- (b) C₁-C₅ alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, aryloxycarbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylalkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C₁-C₈

alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0 - C_6 N-alkyl carbamoyl, C_2 - C_{15} N,N-dialkylcarbamoyl, C_3 - C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3 - C_7 heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) -{CH₂}_s-NR³⁰R³¹, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R³⁰ and R³¹ are each independently hydrogen, cyano, oxo, carboxamido, amidino, C₁-C₈ hydroxyalkyl, C₁-C₃ alkylaryl, aryl-C₁-C₃ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, aryloxycarbonyl, aryl-C₁-C₃ alkoxycarbonyl, C₂-C₈ acyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R³⁰ and R³¹ taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0034] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 10-12 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes the following:



[0035] A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0036] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (i.e., R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (i.e., NH₂-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom.

The term "amino" is meant to include NH₂, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0037] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

[0038] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH₂-) substituted with oxygen to form carbonyl - CO-).

[0039] An "unsubstituted" moiety as defined above (e.g., unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0040] Preferred embodiments of a particular genus of compounds of the invention include combinations of preferred embodiments. For example, paragraph [0042] identifies a preferred Ay¹ and paragraph [0046] identifies preferred Ar¹ (both for compound (1) of paragraph [0041]). Thus, another preferred embodiment includes those compounds of formula (1) in paragraph [0041] in which Ay¹ is as defined in paragraph [0042] and Ar¹ is as defined in paragraph [0046].

Compounds

[0041] In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):

$$R^3$$
 N
 N
 N
 Y^1
 N
 $Y^2 - Ak^1 - Ar^1 - Z^1$
(1)

and pharmaceutically acceptable salts thereof, wherein

 R^3 and R^4 are independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and L^1 - Cy^1 , wherein

L1 is C1-C6 alkyl, C2-C6 heteroalkyl, or C3-C6 alkenyl; and

Cy¹ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

R³ and R⁴ are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally forms part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted:

 Y^1 is selected from the group consisting of -N(R¹)(R²), -CH₂-C(O)-N(R¹)(R²), halogen, and hydrogen, wherein

R¹ and R² are independently selected from the group consisting of hydrogen, L¹, Cy¹, and -L¹-Cy¹, wherein

L¹ is C₁-C₆ alkyl, C₂-C₆ heteroalkyl, or C₃-C₆ alkenyl; and

Cy¹ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

R¹ and R² are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally may form part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

 Y^2 is a chemical bond or N(R⁰), where R⁰ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

 Ak^1 is C_1 - C_6 alkylene, C_1 - C_6 -heteroalkylene (preferably, in which one - CH_2 - is replaced with -NH-, and more preferably -NH- CH_2 -), C_2 - C_6 alkenylene or C_2 - C_6 alkynylene;

 Ar^1 is arylene or heteroarylene, either of which optionally is substituted; and Z^1 is selected from the group consisting of

wherein Ay¹ is aryl or heteroaryl, which optionally is substituted.

[0042] Preferably in the compounds according to paragraph [0041], Ay¹ is phenyl or thienyl, each substituted with -OH or -NH₂.

[0043] More preferably in the compounds according to paragraph [0041], Ay¹ is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay² is attached.

[0044] More preferably in the compounds according to paragraph [0041], Ay¹ is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0045] In some preferred embodiments of the compounds according to paragraph [0041], Z¹ is

[0046] In some preferred embodiments of the compounds according to paragraph [0041], Ar^1 is phenylene. In some embodiments, Ak^1 is alkylene, preferably methylene. In some preferred embodiments, Y^2 is -NH-. In some preferred embodiments, Y^1 is -N(R^1)(R^2) or -CH₂-C(0)-N(R^1)(R^2).

[0047] In some embodiments of the compounds according to paragraph [0041], R^1 and R^2 are each independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-L^1-Cy^1$. In some embodiments, R^1 and/or R^2 is hydrogen. In other embodiments, R^1 and/or R^2 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^1 and/or R^2 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R^1 and/or R^2 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

[0048] In some embodiments of the compounds according to paragraph [0041], R^3 and R^4 are each independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-L^1-Cy^1$. In some embodiments, R^3 and/or R^4 is hydrogen. In other embodiments, R^3 and/or R^4 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^3 and/or R^4 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings.

Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R³ and/or R⁴ is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

[0049] As set forth above, L^1 is C_1 - C_6 alkyl, C_2 - C_6 heteroalkyl, or C_3 - C_6 alkenyl. However, one skilled in the art will understand that when L^1 is not a terminal group, then L^1 is C_1 - C_6 alkylene, C_2 - C_6 heteroalkylene, or C_3 - C_6 alkenylene. In some embodiments, L^1 is alkylene, preferably methylene or ethylene. In other embodiments, L^1 is alkenyl, preferably allyl. In some embodiments, C_3 - C_6 is the radical of a heterocyclic group including, without limitation, piperidine, pyrrolidine, piperazine, and morpholine, each of which optionally is substituted and optionally is fused to one or more aryl rings. In other embodiments C_3 - C_4 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl. In still other embodiments, C_3 - C_4 is aryl or heteroaryl, e.g., phenyl, pyridyl, or pyrrolyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, C_3 - C_4 is fused to one or two benzene rings. In some embodiments, C_3 - C_4 alkyl, C_3 - C_4 alkoxy, and halo. Examples of preferred substituents include methyl, methoxy, and fluoro.

[0050] In some embodiments of the compounds according to paragraph [0041], R¹ and R² and/or R³ and R⁴ are taken together with the adjacent nitrogen atom to form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring optionally is substituted, and optionally is fused to one or more aryl rings. In some preferred embodiments, R¹ and R² and/or R³ and R⁴ are taken together with the adjacent nitrogen atom to form a ring such as, for example, pyrrolidine, piperidine, piperazine, and morpholine, wherein the ring optionally is substituted, and optionally is fused to an aryl ring. In some embodiments, the ring comprising R¹ and R² or R³ and R⁴ is fused to a benzene ring. In some embodiments, the ring comprising R¹ and R² or R³ and R⁴ has a substituent comprising an aryl or cycloalkyl ring, either of which optionally is substituted and optionally is fused to a cycloalkyl, aryl, heteroaryl, or heterocyclic ring. Preferred substituents include, without limitation, phenyl, phenylmethyl, and phenylethyl, the phenyl ring of which optionally is fused to a cycloalkyl, aryl, or heterocyclic ring.

[0051] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of formula 1(a):

(la)

and pharmaceutically acceptable salts thereof, wherein

J is C_1 - C_3 -hydrocarbyl, -N(R^{20})-, -N(R^{20})-CH $_2$ -, -O-, or -O-CH $_2$ -;

R²⁰ is -H or -Me;

X and Y are independently selected from -NH₂, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A-(C₁-C₆-alkyl)_n-B-;

A is H, C₁-C₆-alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -0-, or a direct bond; and

n is 0 (in which case A is directly bonded to B) or 1.

[0052] Preferably in the compounds according to paragraph [0051], A is phenyl optionally substituted with one or more moieties selected from halo (preferably chloro) and methoxy, and B is - NH-. In another preferred embodiment, A is selected from cyclopropyl, pyridinyl, and indanyl.

[0053] Preferably in the compounds according to paragraph [0051], J is -NH-CH₂-, -O-CH₂-, -N(CH₃)-CH₂-, -CH=CH-, or -CH₂-CH₂-.

[0054] Preferably in the compounds according to paragraph [0051], R²⁰ is -H.

[0055] In the compounds according to paragraph [0051] X is preferably selected from

NH,		NH,	D—NH,
		-OMe,	NH,
○ N	-NH ₂	CI	\\\
MeO N H	OMe	OMe MeO NH	
and			

and Y is preferably selected from

-NH₂,	D—NH,	△ H N ,	n-BuNH,
MeOCH₂CH₂NH,	HN CI	HN ,	CI HN-
OMe OMe HN	OMe	HZ ,	Ŷ,
-H	Ме	-OMe	CH ₃ (CH ₂) ₃ NH-
and	CH ₃ O(CH ₂) ₂ -NH		

[0056] In a more preferred embodiment of the compounds according to paragraph [0051], the HDAC inhibitors of the invention comprise the following compounds of formula 1a:

Cpd	J	X	Υ
204	-NH-	NH-NH	-NH ₂
207	-OCH₂-	NH NH	-NH ₂
210	-NHCH₂-		-H
212	-NHCH ₂ -	-OMe	-OMe
214	-NHCH ₂ -	NH-NH	-OMe
216	— N—СН ₂ - СН ₃	NH-NH	-Me
218	-NHCH₂-	NH NH	-Me
220	-CH=CH-	-NH ₂	-NH ₂ -
223	-CH=CH-	\bigcirc N	-NH ₂
224	-CH ₂ CH ₂ -	-NH₂	-NH ₂
470	-NHCH₂-	H	NH ₂
471	-NHCH₂-		<u></u> р—и́н
472	-NHCH₂-	NH NH	△ H N

Cpd	l J	X	Υ
473	-NHCH₂-	□ NH NH	n-BuNH
474	-NHCH₂-		MeO(CH2)₂NH
475	-NHCH₂-	D—ŃH	HN
476	-NHCH₂-	D—NH	OMe HN
477	-NHCH₂-	D—v́H	HN CI
478	-NHCH₂-	 NH	OMe
479	-NHCH₂-	D—NH	OMe HN

Cpd	J	X	Υ
480	-NHCH₂-	D-NH	HN N
481	-NHCH₂-	 	HN
482	-NHCH₂-		D—и́н

Cpd	J	Х	Υ
483	-NHCH ₂ -		Me
484	-NHCH ₂ -		NH ₂
		and	•
485	-NHCH₂-	NH NH	? .

[0057] In a second aspect, the novel histone deacetylase inhibitors of the invention are represented by formula (2):

$$Cy^2-X^1-Ar^2$$
 R^5
 R^6
 R^6

and pharmaceutically acceptable salts thereof, wherein

Cy² is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X¹ is selected from the group consisting of a covalent bond, M¹-L²-M¹, and L²-M²-L² wherein

 L^2 , at each occurrence, is independently selected from the group consisting of a chemical bond, C_1 - C_4 alkylene, C_2 - C_4 alkenylene, and C_2 - C_4 alkynylene, provided that L^2 is not a chemical bond when X^1 is M^1 - L^2 - M^1 :

 M^1 , at each occurrence, is independently selected from the group consisting of -O-, -N(R⁷)-, -S-, -S(O)-, S(O)₂-, -S(O)₂N(R⁷)-, -N(R⁷)-S(O)₂-, -C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-O-and -O-C(O)-NH-, wherein R⁷ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

M² is selected from the group consisting of M¹, heteroarylene, and heterocyclylene, either of which rings optionally is substituted;

Ar2 is arylene or heteroarylene, each of which is optionally substituted;

 ${\sf R}^{\sf 5}$ and ${\sf R}^{\sf 6}$ are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

q is 0 or 1; and

Ay² is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which Ay² is attached) and further optionally substituted;

provided that when Cy^2 is naphthyl, X^1 is $-CH_2$, Ar^2 is phenyl, R^5 and R^6 are H, and q is 0 or 1, Ay^2 is not phenyl or o-hydroxyphenyl.

[0058] In a preferred embodiment of the compounds according to paragraph [0057], when Ay² is o-phenol optionally substituted by halo, nitro, or methyl, Ar² is optionally substituted phenyl, X¹ is -0-, -CH₂-, -S-, -S-CH₂-, -S(O)-, -S(O)₂-, -C(O)-, or -OCH₂-, then Cy² is not optionally substituted phenyl or naphthyl.

[0059] In another preferred embodiment of the compounds according to paragraph [0057], when Ay^2 is o-anilinyl optionally substituted by halo, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy or -NO₂, q is 0, Ar² is phenyl, and X^1 is -CH₂-, then Cy^2 is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).

[0060] In another preferred embodiment of the compounds according to paragraph [0057], when X^1 is -CH₂-, Ar² is optionally substituted phenyl, q is 1, and R⁶ is H, then Cy² is not optionally substituted imidazole.

[0061] In another preferred embodiment of the compounds according to paragraph [0057], when Ar^2 is amino or hydroxy substituted phenyl, X^1 is $C_0 \cdot C_8$ -alkyl- X^{1a} - $C_0 \cdot C_8$ -alkyl, wherein X^{1a} is -CH₂-, -O-, -S-, -NH-, -C(O)-, then Cy^2 is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.

[0062] In another preferred embodiment of the compounds according to paragraph [0057], when Ay^2 is o-phenol, Ar^2 is substituted phenyl, X^1 is -0-, -S-, -CH₂-, -0-CH₂-, -S-CH₂-, or -C(0)-, and R^5 and R^6 are H, then Cy^2 is not optionally substituted naphthyl.

[0063] In another preferred embodiment of the compounds according to paragraph [0057], when Ay^2 is o-anilinyl, q is 0, Ar^2 is unsubstituted phenyl, X^1 is -CH₂-, then Cy^2 is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.

[0064] Preferably in the compounds according to paragraph [0057], Ay² is phenyl or thienyl, each substituted with -OH or -NH₂.

[0065] More preferably in the compounds according to paragraph [0057], Ay² is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay² is attached.

[0066] More preferably in the compounds according to paragraph [0057], Ay² is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0067] In a another embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0057] wherein

q is 1; -

 M^1 , at each occurrence, is selected from the group consisting of -N(R^7)-, -S-, -C(O)-NH-, and -O-C(O)-NH-, where R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and

Ay2 is anilinyl, which optionally is substituted.

[0068] In some preferred embodiments of the compounds according to paragraph [0067], the $-NH_2$ group of Ay^2 is in an ortho position with respect to the nitrogen atom to which Ay^2 is attached. In some embodiments, R^5 and R^6 are independently selected from the group consisting of hydrogen and C_1 - C_4 alkyl. In some preferred embodiments, R^5 and R^6 are hydrogen.

[0069] In some embodiments of the compounds according to paragraph [0067], Ar² has the formula

wherein G, at each occurrence, is independently N or C, and C optionally is substituted. In some preferred embodiments, Ar² has the formula

[0070] In some preferred embodiments of the compounds according to paragraph [0069], Ar² is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolylene.

[0071] In some embodiments of the compounds according to paragraph [0067], X^1 is a chemical bond. In some embodiments, X^1 is L^2 - M^2 - L^2 , and M^2 is selected from the group consisting of -NH-, -N(CH₃)-, -S-, -C(O)-N(H)-, and -O-C(O)-N(H)-. In some embodiments, X^1 is L^2 - M^2 - L^2 , where at least one occurrence of L^2 is a chemical bond. In other embodiments, X^1 is L^2 - M^2 - L^2 , where at least one occurrence of L^2 is alkylene, preferably methylene. In still other embodiments, X^1 is L^2 - M^2 - L^2 , where at least one occurrence of L^2 is alkenylene. In some embodiments, X^1 is M^1 - L^2 - M^1 and M^1 is selected from the group consisting of -NH-, -N(CH₃)-, -S-, and -C(O)-N(H)-.

[0072] In some embodiments of the compounds according to paragraph [0067], Cy² is aryl or heteroaryl, e.g., phenyl, pyridyl, imidazolyl, or quinolyl, each of which optionally is substituted. In some embodiments, Cy² is heterocyclyl, e.g.,

each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy² has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl.

[0073] In a preferred embodiment of the compounds of paragraph [0057], the invention comprises compounds of structural formula (2a):

and pharmaceutically acceptable salts thereof, wherein

Ara is phenyl or thienyl;

 R^6 is H, or C_1 - C_6 -alkyl (preferably - CH_3);

Y and Z are independently -CH= or -N=;

W is halo, (V'-L⁴)_t-V-L³-;

 L^3 is a direct bond, $-C_1-C_6$ -hydrocarbyl, $-(C_1-C_3-hydrocarbyl)_{m_1}-X'-(C_1-C_3-hydrocarbyl)_{m_2}$, -NH-($C_0-C_3-hydrocarbyl$), ($C_1-C_3-hydrocarbyl$)-NH-, or -NH-($C_1-C_3-hydrocarbyl$)-NH-;

m1 and m2 are independently 0 or 1;

X' is $-N(R^{21})$ -, $-C(O)N(R^{21})$ -, $N(R^{21})C(O)$ -, -O-, or -S-;

 R^{21} is -H, V"-(C₁-C₆-hydrocarbyl)_c;

L⁴ is (C₁-C₆-hydrocarbyl)_a-M-(C₁-C₆-hydrocarbyl)_b;

a and b are independently 0 or 1;

M is -NH-, -NHC(0)-, -C(0)NH-, -C(0)-, -SO₂-, -NHSO₂-, or -SO₂NH-

V, V', and V'' are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the \mathcal{A} and Ar^a rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

[0074] In a preferred embodiment of the compound according to paragraph [0073]:

Y and Z are -CH =and R^6 is H;

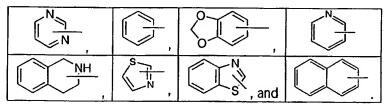
W is V-L3;

L3 is -NH-CH- or -CH-NH-;

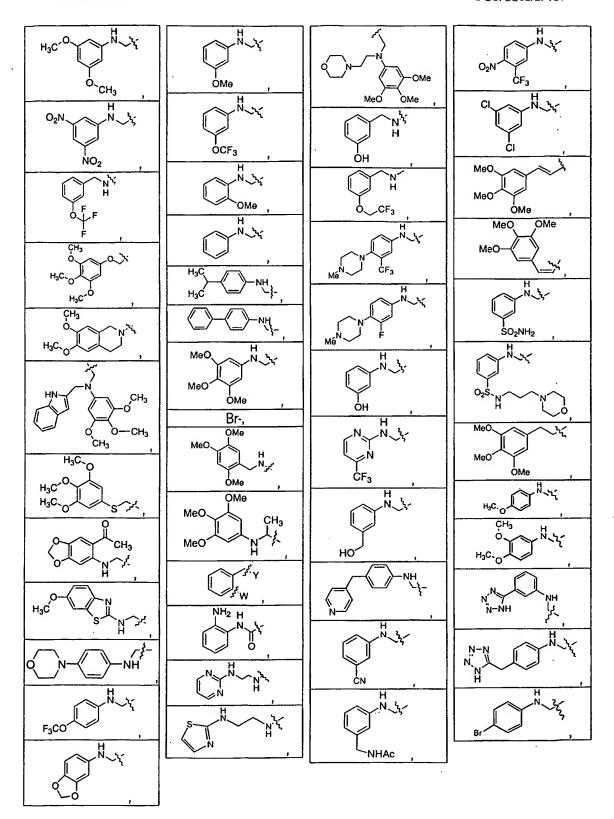
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, C_1 - C_6 -hydrocarbyl, C_1 - C_6 -hydrocarbyl-oxy or -thio (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

Ara is phenyl and the amino moieties to which it is bound are ortho to each other.

[0075] In some preferred embodiments of the compound according to paragraph [0073], V is an optionally substituted ring moiety selected from:



[0076] In another preferred embodiment of the compounds according to paragraph [0073], W is selected from:,



[0077] In another preferred embodiment of the compounds according to paragraph [0073], the \mathcal{A} and Ara rings are not further substituted.

[0078] In a particularly preferred embodiment of the compounds according to paragraph [0073], the compounds of the invention are selected from the following, in which, unless expressly displayed otherwise, Ar^a is phenyl (and, preferably, the amide nitrogen and the amino nitrogen bound to Ar^a are *ortho* to each other):

Cpd	W	Υ	Z	R ⁶
481	H ₃ C O H ₃ C, O H ₃ 't,	СН	СН	Н
484	H ₃ C-0 H ₃ C-0 H ₃ C-0		H Y ^{N⊦}	12
492	H ₃ C O CH ₃	СН	сн	Н

Cpd	W	Υ	Z	R ⁶
493	CI N N N N N N N N N N N N N N N N N N N	СН	СН	Ξ
494	H ₃ C ^{-O} CH ₃	СН	сн	Н
495	O ₂ N H N - ½;	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
496	W N'''s H OFF F	СН	СН	Н
497	CH ₃ O C C H ₃ C O C C	СН	СН	Н
498	H ₃ C _O	СН	СН	Н
499	HN CH ₃ CCH ₃	СН	СН	Н
500	H ₃ C O S S	СН	СН	Н
501	O T N T	СН	СН	Н
502	O-CH ₃	СН	СН	Н
503	O_N-{}-NH	СН	СН	Н
504	F ₃ CO H	СН	СН	Н
505		СН	СН	Н
506	OCF ₃	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
507	H N Y	СН	СН	Н
508	H N '''' _Y '	СН	СН	Н
509		СН	СН	Н
510	H ₂ C H ₃	СН	СН	Н
511	NH -	СН	СН	Н
512	MeO H N '\\\ MeO OMe	СН	N	Н
516	Br-	СН	СН	CH₃
517	OMe MeO H N _j ,r,r	СН	СН	СН₃
518	OMe OMe MeO MeO NeO NeO	СН	сн	СН₃
519	J.F.W	СН	СН	Н
520	NH ₂ H	СН	СН	Н
521	N N N N N N N N N N N N N N N N N N N	N	СН	H
522	S N N N N N N N N N N N N N N N N N N N	N	СН	Н
523	N—N—OMe MeO OMe	СН	СН	H

Cpd	W	Y	Z	R ⁶
524	OH CH	N	СН	Н
525	N ² Y	N	СН	Н
526	MeN N—NH CF ₃	СН	СН	Н
527	Men N NH	СН	СН	Н
528	H N Ž	СН	СН	Н
529	N N N N N N N N N N N N N N N N N N N	СН	СН	Н
530	HO	СН	СН	Н
531	NH F	СН	СН	Н
532	NC H	СН	СН	Н
533	NHAC NHAC	СН	CH	Н
534	O ₂ N CF ₃	СН	СН	Н
535	CI H Z Z Z	СН	СН	Н

Cpd	W	Y	Z	R ⁶
536	MeO MeO OMe	СН	СН	Н
537	MeO	СН	СН	Н
538	SO ₂ NH ₂	СН	СН	Н
539	D ₂ S ₂ N	СН	СН	Н
540	MeO VIZ	СН	СН	Н
541	H ₃ C ₀ H ₂ Z ₄	СН	СН	Н
542	H ₃ C H N 2\(\frac{1}{2}\)	СН	СН	Н
543	N 252	СН	СН	н
544	N-N H H N-24	СН	СН	Н
545	Br N-Y	СН	СН	Н
546	H N Vi	СН	СН	Н
547	, N. Y.	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
548	P N JY	СН	СН	Н
549	O OH	СН	СН	Н
550	O ₂ N Y	СН	СН	Н
551	H 74	СН	СН	Н
552	CI N. Y.	СН	СН	Н
553	المرابع المراب	СН	СН	Н
554	المرابع	CH	СН	Н
555	IN SMB	СН	СН	Н
556	Mes H Z	СН	СН	Н
557	B. N. T. Y.	СН	СН	Н
558		СН	CH	Н
559	F \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
560	MeO H N OMe		H	lH2
561	MeO H		NH₂	
562	MeO H N \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	СН	СН	Н
563	OMe OMe HN OMe	CH	СН	Н
564	MeO H		NH ₂	
565	H ₃ C. _S	СН	СН	Н
566	F F N Z	СН	СН	Н
567	MeO H H N N N N N N N N N N N N N N N N N		I XNH ₂	
568	MeO H ₂ N		-	H ₂

Cpd	W	Υ	Z	R ⁶
569	H ₃ C O	СН	N	Н

Cpd	W	Y Z R ⁶
570	CH ₃ O NH	H ₂ N HN S

[0079] In a preferred embodiment of the compounds according to paragraph [0057], the invention comprises compounds of the formula (2b):

$$Cy^2 \times 1$$

$$Q \qquad N - Ay^2$$
(2b)

and pharmaceutically acceptable salts thereof, wherein

 Ay^2 is phenyl or thienyl, each substituted at the ortho position with -NH₂ or -OH and each further optionally substituted with one to three substituents independently selected from -NH₂, -OH, and halo;

q is 0 or 1;

X¹ is selected from -CH₂-, -NH-CH₂-, and -S-CH₂-;

 Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3 -, CH_3O -, phenyl optionally substituted with one to three CH_3O -, morphylinyl, morphylinyl- C_3 -alkoxy, cyano, and $\text{CH}_3\text{C}(0)\text{NH}$ -;

provided that when Cy^2 is naphthyl, X^1 is $-CH_{2^*}$, and q is 0 or 1, Ay^2 is not o-hydroxyphenyl. [0080] Preferably in the compounds according to paragraph [0079], Ay^2 is selected from:

$$NH_2$$
 OH NH_2 and NH_2

[0081] Preferably in the compounds according to paragraph [0079], Cy² is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinozolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH₃O-. More preferably, Cy² is phenyl substituted with one to three CH₃O-.

[0082] In a third embodiment, the novel inhibitors of histone deacetylase are represented by formula (3):

$$Cy^3-X^2-Ar^3 \qquad NH \qquad NH_2 \qquad (3)$$

and pharmaceutical salts thereof, wherein

Ar3 is arylene or heteroarylene, either of which optionally is substituted;

Cy³ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted;

provided that when Cy^3 is a cyclic moiety having -C(0)-, -C(S)-, -S(0)-, or -S(0)₂- in the ring, then Cy^3 is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

 X^2 is selected from the group consisting of a chemical bond, L^3 , W^1-L^3 , L^3-W^1 , $W^1-L^3-W^1$, and $L^3-W^1-L^3$, wherein

W¹, at each occurrence, is S, O, or N(R⁹), where R⁹ is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

 L^3 is C_1 - C_4 alkylene, C_2 - C_4 alkenylene, or C_2 - C_4 alkynylene;

provided that X^2 does not comprise a -C(0)-, -C(S)-, -S(0)-, or -S(0)₂- group; and further provided that when Cy³ is pyridine, then X^2 is L³, W¹-L³, or L³-W¹.

[0083] Preferably, Ar³ has the structure:

wherein Q, at each occurrence, is independently N or C, and C optionally is substituted.

[0084] Preferably in the compounds according to paragraph [0082], X² is selected from the group consisting of L³, W¹-L³-W¹, W¹-L³-W¹, and L³-W¹-L³.

[0085] Preferably in the compounds according to paragraph [0082], when X^2 is a chemical bond, then Ar^3 is not

and Cy³ is not the radical of a substituted or unsubstituted diazepine or benzofuran.

[0086] In some embodiments of the compounds according to paragraph [0082], Q at each occurrence is C(R⁸), where R⁸ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. In some other embodiments, from one to about three variables Q are nitrogen. In some preferred embodiments, Ar³ is selected from the group consisting of phenylene, pyridylene, thiazolylene, and quinolylene.

[0087] In some embodiments of the compounds according to paragraph [0082], X^2 is a chemical bond. In other embodiments, X^2 is a non-cyclic hydrocarbyl. In some such embodiments, X^2 is alkylene, preferably methylene or ethylene. In other such embodiments, X^2 is alkenylene or alkynylene. In still other such embodiments, one carbon in the hydrocaryl chain is replaced with -NH- or -S-. In some preferred embodiments, X^2 is $W^1+L^3-W^1$ and W^1 is -NH- or -N(CH₃)-.

[0088] In some embodiments of the compounds according to paragraph [0082], Cy³ is cycloalkyl, preferably cyclohexyl. In other embodiments, Cy³ is aryl or heteroaryl, e.g., phenyl, pyridyl, pyrimidyl, imidazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the cyclic moiety of Cy³ is fused to a benzene ring. In some embodiments, Cy³ has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl. Some other preferred substituents have the formula –K¹-N(H)(R¹⁰), wherein

K1 is a chemical bond or C1-C4 alkylene;

 R^{10} is selected from the group consisting of Z' and -Ak²-Z', wherein

Ak² is C₁-C₄ alkylene; and

Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

[0089] Examples of such preferred substituents according to paragraph [0088] include

[0090] In some embodiments of the compounds according to paragraph [0082], Cy³ is heterocyclyl, e.g.,

each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the heterocycle of Cy³ is fused to a benzene ring.

[0091] Preferably in the compounds of paragraph [0082], when Ar^4 is quinoxalinylene, then X^3 is not -CH(OH)-.

[0092] In another preferred embodiment, Ar³ is

wherein X is -CH₂-, -NH-, O, or S. Preferably Ar³ is

and X is S or O.

[0093] In a preferred embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0057] wherein

Ay2 is ortho-anilinyl;

q is 0; and

 X^1 is $M^1-L^2-M^1$ or $L^2-M^2-L^2$.

[0094] In a preferred embodiment of the compounds according to paragraph [0093], Ar² is arylor heteroaryl; and Cy²-X¹- is collectively selected from the group consisting of

- a) A₁-L₁-B₁-, wherein A₁ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁ is -(CH₂)₀₋₁NH(CH₂)₀₋₁-, -NHC(O)-, or -NHCH₂-; and wherein B₁ is phenyl or a covalent bond;
- b) A₂-L₂-B₂, wherein A₂ is CH₃(C=CH₂)-, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L₂ is -C≡C-; and wherein B₂ is a covalent bond;

c) A₃-L₃-B₃, wherein A₃ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₃ is a covalent bond; and wherein B₃ is – CH₂NH-;

- d) $A_4-L_4-B_4-$, wherein A_4 is an optionally substituted aryl; wherein L_4 is $-NHCH_2$; and wherein B_4 is a thienyl group;
- e) A₅-L₅-B₅-, wherein A₅ is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₅ is a covalent bond; and wherein B₅ is -SCH₂-;
- f) morpholinyl-CH₂-
- g) optionally substituted aryl;
- h) A₆-L₆-B₆-, wherein A₆ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₆ is a covalent bond; and wherein B₆ is NHCH₂-;
- i) $A_7L_7B_7$, wherein A_7 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_7 is a covalent bond; and wherein B_7 is $-CH_2$ -;
- j) aptionally substituted heteroaryl or optionally substituted heterocyclyl;
- k) A_8L_8 - B_8 -, wherein A_8 is optionally substituted phenyl; wherein L_8 is a covalent bond; and wherein B_8 is -0-;
- A₉-L₉-B₉-, wherein A₉ is an optionally substituted aryl; wherein L₉ is a covalent bond; and wherein B₉ is a furan group;
- m) A_{10} - L_{10} - B_{10} -, wherein A_{10} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{10} is -CH(CH₂CH₃)-; and wherein B_{10} is -NHCH₂-;
- n) A₁₁-L₁₁-B₁₁-, wherein A₁₁ is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₁ is a covalent bond; and wherein B₁₁ is –OCH₂-;
- o) A₁₂-L₁₂-B₁₂-, wherein A₁₂ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₂ is-NHC(O)-; and wherein B₁₂ is N(optionally substituted aryl)CH₂-;
- A₁₃-L₁₃-B₁₃-, wherein A₁₂ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₃ is a covalent bond; and wherein B₁₃ is NHC(O)-;

q) A_{14} - L_{14} - B_{14} , wherein A_{14} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{14} is-NHC(0)(optionally substituted heteroaryl); and wherein B_{14} is -S-S-;

- r) F₃CC(0)NH-;
- s) A₁₅-L₁₅-B₁₅-, wherein A₁₅ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₅ is-(CH₂)₀₋₁NH(optionally substituted heteroaryl)-; and wherein B₁₅ is –NHCH₂-;
- t) A₁₆-L₁₆-B₁₆-, wherein A₁₆ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₆ is a covalent bond; and wherein B₁₆ is N(optionally substituted alkyl)CH₂-; and
- u) A₁₆-L₁₆-B₁₆-, wherein A₁₆ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₆ is a covalent bond; and wherein B₁₆ is (optionally substituted aryl-CH₂)₂-N-.

[0095] In another preferred embodiment of the compounds according to paragraph [0093], Cy^2 - X^1 - is collectively selected from the group consisting of

- a) D₁-E₁-F₁-, wherein D₁ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E₁ is -CH₂- or a covalent bond; and wherein B₁ is a covalent bond;
- b) D_2 - E_2 F₂-, wherein D_2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_2 is $-NH(CH_2)_{0\cdot 2^*}$; and wherein F_2 is a covalent bond;
- c) $D_3 E_3 F_3$, wherein D_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_3 is $-(CH_2)_{02}NH$ -; and wherein F_3 is a covalent bond:
- d) D_4 - E_4 - F_4 -, wherein D_4 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_4 is $-S(CH_2)_{0.2}$ -; and wherein F_4 is a covalent bond:
- e) D₅-E₅-F₅-, wherein D₅ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E₅ is –(CH₂)₀₋₂S-; and wherein F₅ is a covalent bond; and

f) D_6 - E_6 - F_6 , wherein D_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_6 is -NH(CH₂)₀₋₂NH-; and wherein F_6 is a covalent bond.

[0096] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0057] having formula (3b):

and pharmaceutically acceptable salts thereof, wherein Y and Z are independently N or CH and W is selected from the group consisting of:

N H	H ₃ Ç // \	
N H L	н₃с он	}-
CI NH	NH ₂ H	MeO H H
MeO H	H ₂ C CH ₃	ОН
CI NH NH	S NH	MeO OMe
N H S S	N H S S	N N H
O N Sir	MeO Yaya	NH2 N N N N N N N N N N N N N N N N N N N
HN N N N N N N N N N N N N N N N N N N	HN N N N N N N N N N N N N N N N N N N	N HIN Y
	H Z Z H	CI N St Me

	· · · · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·
N St.	MeO N N N	F N N
O N,CH3 CH3		Br N Sr.
S N N N N N N N N N N N N N N N N N N N	N O OMe	Br N pr
Br N O	Br N , r.	CI N N N
F N N SP.	F F N N S	S N N
N - \\ \\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	Me N	N N N
N N N	H ₃ C O,N	N N N
N N N	NC HN—S	NC Me
H CN S Me		
	OH OH	O ['] irir

MeO Contraction of the contracti	MeO N	CI CH ₃
Br NH NH OME	MeO ONE OME	CI—NH —OMe
ONH OME	O N N OME	NH ₂ H
N N ZZ	H ₃ C N S Y	F N S ZZ
NH ₂ H	N S St.	CH ₃ N N N N N N N N N N N N N N N N N N N
H3C N N N	CH ₃	H ₃ C ₂ O ₃ C
O H	H3C ON N	H ₃ C ^O N N N N N N N N N N N N N N N N N N N
N NH NH	H ₃ C _O NNNort	S. J.
H ₃ C ^{-O} H N N N N N N N N N N N N N N N N N N	H ₃ C CH ₃	O _{CH3}
H ₃ C-O-\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	\(\)\(\)\(\)\(\)\(\)\(\)\(\)\(\)\(\)\(\	H ₃ C' Q H ₃
O NH NH ₂	Z HZ	0 H N 34

H ₃ C N N N	N H N Z	H ₃ C N 7/1
H ₃ C ₋₀ H ₃ C ₋₁	H ₃ C ₀ H ₃ C ₁	H ₃ C O H
H ₃ C H ₃	H 34;	H ₃ C H ₃ H \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \
H ₃ C C C H	ON N N N N N N N N N N N N N N N N N N	MeO N N N N N N N N N N N N N N N N N N N
F H	MeO H	H N is
N- ¹ / _F	H N V	CI H N ''',
CI H N ZZ	H N N N N N N N N N N N N N N N N N N N	MeO N H
F ₃ CO H N 12-	H N Vi ₂	MeO OMe
OCF ₃	F ₃ CO H +	MeO H
	H N OMe	H N N V ₃ -
F ₃ C N ¹ ,	MeO OMe	MeO H N N N N N N N N N N N N N N N N N N

		Н
MeO N-3-	ON N H N N	HN N Y'
MeS H N Zz	H N N N SMe	MeO H N Ya,
MeO H H N 14	MeO HN N	MeO OMe H N N N N N N N N N N N N N N N N N N
H ₃ C CH ₃ H ₃ C CH ₃ H ₃ C CH ₃ N N N N OMe	OH N 225	N N N N N N N N N N N N N N N N N N N
F ₃ CO N ¹ V ₁	MeO H N 't,	O NH Ti
O NH NH NA	MeO HNH NH ₂	O NH NH NH
MeO H ₂ N H ₂ N	MeO NH '\'\'	OI, ONH, Y'
N-N-NH,	ОН	H ₃ C
HiN	N N N N N N N N N N N N N N N N N N N	HN-N H
MeO H	ОН	OMe

F N	OMe	MeO
MeO	MeO_N_N OMe	
MeO	C S S S S S S S S S S S S S S S S S S S	F N
MeO N N N N N N N N N N N N N N N N N N N	N-N Ph O S	H H
	Me No	
H ₃ C N S CH ₃	and	F N S

[0097] In a preferred embodiment of the compounds according to paragraph [0096], the compounds comprise those wherein Y, Z and W are as defined below:

Cpd	W	Y	Z
164	MeO H	СН	СН
165	но	N	СН
166	MeO-	СН	СН
167	MeO	СН	N
168	MeO H	СН	N
169	MeO N N	СН	СН

Cpd	W	Υ	Z
170		СН	СН
171	MeO S	N	СН
172	S S S	СН	СН
174	EZ F	СН	N
175	F	СН	N
176	MeO NH	СН	N
177	Ph N-N S	СН	СН
178		N	СН

Cpd	W	Υ	Z
179	N N	СН	СН
180	Me No	СН	СН
181		СН	СН
182	H ₃ C N S N CH ₃	СН	СН
	and		
183	F	СН	СН

[0098] In another preferred embodiment of the compounds according to paragraph [0096], the compounds comprise those wherein Y, Z and W are as defined below:

Cpd	W	Υ	Z
187	N H	СН	сн
188	NH ₂ H	СН	СН
189	MeO H H H	СН	СН
190	MeO H	СН	СН
193	H ₂ C CH ₃	СН	СН
194	ОН	СН	СН
195	н₃с он	СН	СН
196	<u> </u>	СН	СН
320	CI NH	СН	СН
321	CI NH	СН	СН
322	S NH	СН	СН
323	MeQ OMe MeO S	СН	СН

	s defined below.			
Cpd	W	Y	Z	
325	N H S S	ĊН	СН	
326	N N S S	СН	СН	
327	N	СН	СН	
328	ON JA	СН	СН	
329	MeO OMe	СН	СН	
330	H ₃ C N N N N N N N N N N N N N N N N N N N	СН	СН	
331	HN NH2	СН	СН	
332	HN N N N	СН	СН	
333		СН	СН	
334	H NH	СН	СН	
335		СН	СН	

Cpd	W	Y	Z
336	CI N Me	СН	СН
337	N Me	СН	СН
338	MeO N N Jr	СН	СН
339	F N Jrt	СН	СН
340	ON CH ₃	СН	СН
341		СН	СН
342	Br N pr	СН	СН
343	S H N O	СН	СН
344	Br N St	СН	СН
345	ONE OME	СН	СН
346	Br N , r	СН	СН

Cpd	W	Υ	Z
347	Br N'N	СН	СН
348	CI NEW	СН	сн
349	E N N St.	СН	СН
350	F F N N 3 ^d .	СН	СН
351	S N N	СН	СН
352	N V V N	СН	СН
353	Me N	СН	СН
354		СН	СН
355		СН	СН
356	H ₃ C \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	СН	СН
357	N O N	СН	СН
358	N= N-	СН	СН
359	NC HN S	СН	СН

Cpd	W	Y	Z
360	Ph S NC Me	СН	СН
361	H H CN O S Me	СН	СН
362	o TN T	СН	СН
363	S 0	СН	СН
364		СН	СН
365	он он	СН	СН
366	C) ojvir	СН	СН
367	MeO Contraction	СН	СН
368	MeO N	СН	СН
369	CI CH ₃	СН	СН
370	Br NH O NO NO OMe	СН	СН

Cpd	W	Y	Z
371	MeO O NH OMe	СН	СН
372	CI—NH OME	СН	СН
373	ONH OME	СН	СН
374	O—NH OME	СН	СН
375	NH ₂ H	СН	СН
377	N N ZZ	СН	СН
378	H ₃ C N S Y	СН	СН
379	F N S 3	СН	СН
380	NH ₂ H	N	СН
381	N S St.	СН	СН
382	H ₃ C N N N X	СН	СН

Cpd	W	Υ	Z
383	H ₃ C N N N	СН	СН
384	H ₃ C N O	СН	СН
385	H ₃ C, O Z = Z + Z + Z + Z + Z + Z + Z + Z + Z +	СН	СН
386		сн	СН
387	H ³ C O N N N N N N N N N N N N N N N N N N	СН	СН
388	H ₃ C ^{-O} N N /	СН	СН
389	NH NH	ĊН	СН
390	H³C-O\N N	СН	СН
391		СН	СН
392	H ³ C, O H ³	СН	СН
393	H ₃ C O CH ₃	СН	СН
394	CH3 S	СН	СН

Cpd	W	Υ	Z
395	H ₃ C O CH ₃	СН	СН
396		CH	СН
397	H ₃ C, O H ₃	СН	СН
398	$\bigvee_{NH_2}^{O} \downarrow_{N} \varsigma_{S:} \rbrace_{-}$	СН	N
399	== -{-	сн	СН
400	H N - Y	СН	СН
401	H ₃ C N N N N	СН	СН
402	ON-NH	СН	СН
403	H ₃ C, CH ₃ .	СН	СН
404	H ₃ C ₂	СН	СН
405	N A CO HAY	СН	сн
406	H ₃ C O H O H	СН	СН

Cpd	W	Υ	Z
407	H ₃ C H ₃	СН	СН
408	N=O-NH}	СН	СН
409	H ₃ C	СН	СН
410	CH ₃ H N N ₁	СН	СН
411		СН	СН
412	MeO N-1, H	СН	сн
413	F H	СН	СН
414	MeO H	СН	СН
415	F N Y	СН	СН
416	N-Y H	СН	СН
417	H N V	СН	СН
418		СН	СН

Cpd	W	Υ	Z
419		СН	СН
420	H N N N N N N N N N N N N N N N N N N N	СН	СН
421	MeO N H	СН	СН
422	F ₃ CO H N - ½	СН	СН
423	H N OCF ₃	СН	СН
424b	MeO OMe	СН	СН
425	N- ¹ / ₄ , OCF ₃	СН	СН
426	F ₃ CO N- ¹ / _H	СН	СН
427	MeO H N - 125	СН	СН
428		СН	СН
429	H N OMe	СН	СН
430	H N Vy	СН	СН

Cpd	W	Υ	Z
431	F ₃ C N ² ,	СН	СН
432	MeO OMe	СН	СН
433	MeO H H N N N N N N N N N N N N N N N N N	СН	СН
434	MeO OMe	СН	СН
435		СН	СН
436	HN N Y	СН	СН
437	MeS H N 12-	СН	СН
438	H N 124	СН	СН
439	MeO H N Y	СН	СН
440	MeO HN X	сн	СН
441	H ₃ C O H N N N N N N N N N N N N N N N N N N	СН	СН

Cpd	W	Υ	Z
442	MeO OMe	СН	СН
443	H ₃ C -Si .O N OMe	СН	СН
444	MeO OMe	СН	CH
445	MeO H N L'I	СН	N
446	N H N H N H N H N H N H N H N H N H N H	СН	N
447	F ₃ CO N ^h i	СН	СН
448	H ₃ C N N N N N N N N N N N N N N N N N N N	СН	СН
449	O NH 'Y'	СН	СН
450	S-NHX	СН	СН
451	S-NH.J.	СН	СН
452	N= S-N-INH.X	СН	СН
453	MeO H NH	NH ₂	

Cpd	W	Υ	Z
454	MeO H N	i Ni	H ₂
455	O NH Y	СН	СН
456	MeHN—s NH \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	СН	СН
457	MeO H ₂ N H ₂ N H ₂ N	〉	
458	MeO NH 'T'	СН	СН
459	0, 0 NH, 1-(NH, 1-(СН	СН
460	NH N'ri	СН	N
461	H ₃ C _N NH, X ₁	СН	СН

Cpd	W	Υ	Z
462	HN————————————————————————————————————	СН	СН
463	ОН	N	СН
464	H ₃ C S ¹	N	СН
465	HN	СН	СН
466	N HN S to	СН	СН
467	Br S NH	СН	СН
468	HN-N H	СН	СН

[0099] In yet another a preferred embodiment, the novel histone deacetylase inhibitors of the invention are selected from the group consisting of the following and their pharmaceutically acceptable salts:

H ₃ C H ₃ C-Si	HC NH ₂
CI H ₂ N HN	
CH ₃ S NH O HN H ₂ N	H ₃ C _O S H ₂ N
	O N H NH2
NH CI N NO-CH ₃	H ₃ C N NH ₂
H ₂ N HN N H	NH ₂
S N NH ₂	H ₃ C N NH ₂
H ₃ C N N NH ₂	NH ₂

NH ₂	H H NH ₂
H NH ₂	H ₃ C N NH ₂
HN NH ₂	NH ₂
H ₃ C — N N NH ₂	CH ₃ N CH ₃ N N CH ₃ N N N N N N N N N N N N N N N N N N N
NC S H NH ₂ H-N CH ₃ O	H ₃ C ON NH ₂
OH NH₂	H ₃ C O CH ₃ O N NH ₂ NH ₂ CH ₃
CH ₃ OCH ₃ H ₂ N H ₃ C HN H ₃ C	0 NH ₂ NH ₂ H ₃ C O H ₃ C
MeO H H OH OH	H ₃ C-0 N N NH ₂

H ₃ C-O N NH ₂	MeO N S HO
MeO N S	SMe HN O N H
NH NH ₂	MeO NH O HN S H₂N
MeO H H OH	MeO OMe
DO NO SHOW THE STATE OF THE STA	MeO H NH ₂
H ₂ N H ₃ C	H ₃ C NH NH ₂

[0100] In another preferred embodiment, the compounds are selected from those listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f.

Synthesis

[0101] Compounds of formula (1), wherein Y^1 is $-N(R^1)(R^2)$, preferably may be prepared according to the synthetic route depicted in Scheme 1. Thus, trichlorotriazine I reacts with amine II in the presence of diisopropylethylamine to produce dichloroaminotriazine III. The amine R^1R^2NH is added to dichloroaminotriazine III to produce diaminochlorotriazine V. Treatment of V with ammonia or R^3R^4NH in tetrahydrofuran (THF) or 1,4 dioxane affords triaminotriazine VI.

[0102] Alternatively, dichloroaminotriazine III may be reacted with ammonia gas in 1,4 dioxane to produce diaminochlorotriazine IV. Treatment of IV with R¹R²NH in THF or 1,4 dioxane in a sealed flask then affords triaminotriazine VI.

[0103] Hydrolysis of the ester moiety in VI is effected by treatment with a hydroxide base, such as lithium hydroxide, to afford the corresponding acid VII. Treatment of the acid VII with 1,2-phenylenediamine in the presence of BOP reagent, triethylamine, and dimethylformamide (DMF) yields the anilinyl amide VIII.

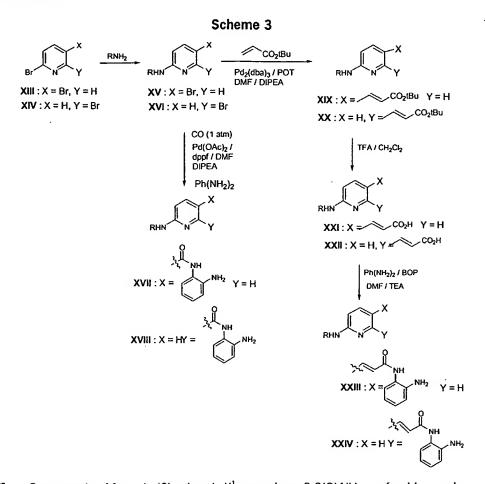
[0104] Compounds of formula (1), wherein Y¹ is -CH₂-C(O)-N(R¹)(R²), preferably may be prepared as outlined in Scheme 2. Thus, piperazine IX is treated with acetyl chloride and triethylamine to produce amide X. Reaction of X with dichloromorpholyltriazine and lithium hexamethyldisiloxane affords compound XI. The chloride of XI is converted to the anilinyl amide of XII as described above with respect to Scheme 1: treatment with the amine and diisopropylethylamine; followed by lithium hydroxide; followed by BOP reagent, phenylenediamine, triethylamine, and DMF.

Scheme 2

[O105] Compounds of formula (2), wherein Ar² is pyridylene and X¹ comprises -N(R⁷)-, compounds of formula (3), wherein Ar³ is pyridylene and X² comprises -N(R⁹)-, and compounds of formula (4), wherein Ar⁴ is pyridylene and X³ comprises -N(R¹¹)-, preferably may be prepared according to the procedures illustrated in Scheme 3. Dibromopyridine XIII or XIV is treated with amine RNH₂ to produce aminobromopyridine XV or XVI, respectively. Treatment of XV or XVI with diacetoxypalladium, diphenylphosphinoferrocene, DMF, diisopropylethylamine, and phenylenediamine under carbon monoxide yields anilinyl amide XVII or XVIII, respectively.

[0106] Treatment of XV or XVI with tert-butylacrylate, diisopropylethylamine, dibenzylacetone palladium, and tri-o-tolylphosphine (POT) in DMF under nitrogen affords compounds XIX and XX, respectively. The ester moiety of XIX or XX is hydrolyzed to produce the corresponding acid moiety in XXI or XXII, respectively, by reaction with trifluoroacetic acid in dichloromethane. Treatment of

the acid XXI or XXII with phenylenediamine, BOP, and triethylamine affords the anilinyl amide XXIII or XXIV, respectively.



[O107] Compounds of formula (2), wherein X¹ comprises -O-C(O)-NH-, preferably may be prepared according to the synthetic route depicted in Scheme 4. Thus, carbinol XXV is added to bromobenzylamine XXVI with carbonyldiimidazole (CDI), triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to produce compound XXVII. The remaining synthetic steps in the production of anilinyl amide XXVIII are as described above for Scheme 3.

Scheme 4

[0108] Compounds of formula (2), wherein X¹ comprises -N(R³)-, preferably may be prepared as outlined in Scheme 5. Amine XXIX is reacted with p-bromobenzylbromide in the presence of potassium carbonate in DMF to produce bromobenzylamine XXX. Treatment of XXX with nitroacrylanilide, dibenzylacetone palladium, POT, and diisopropylethylamine in DMF affords nitroanilide XXXI. Nitroanilide XXXI is converted to the corresponding anilinyl amide XXXII by treatment with stannous chloride in methanol and water.

[0109] Treatment of amine XXXI in formic acid with paraformaldehyde provides methylamine XXXIII. The nitroanilide moiety in XXXIII is then converted to the corresponding anilinyl amide moiety in XXXIV by treatment with stannous chloride in methanol and water.

Scheme 5

[0110] Alternatively, compounds of formula (2), wherein X¹ comprises -N(R²)-, may be prepared according to the synthetic route depicted in Scheme 6. Carboxylic acid XXXV in methanol is treated with hydrochloric acid to produce ester XXXVI. Conversion of the primary amine moiety in XXXVI to the secondary amine moiety in XXXVI is effected by treatment with a catalyst such as triethylamine, methoxybenzylchloride, sodium iodide, and potassium carbonate in DMF at 60 °C. Ester XXXVI is converted to anilinyl amide XXXVII by treatment with sodium hydroxide, THF, and methanol, followed by BOP, triethylamine, and phenylenediamine in DMF, as described above for Scheme 3.

Scheme 6

[0111] Compounds of formula (2), wherein X¹ comprises R or -C(O)-NH-, preferably may be prepared according to the procedures illustrated in Scheme 7. Addition of amine 68 to haloaryl compound XXXVIII or XXXIX and potassium carbonate in DMF provides arylamine XL or XLI, respectively. Anilinyl amide XLII or XLIII is then prepared using procedures analogous to those set forth in Schemes 3-6 above.

Scheme 7

$$Ar-Z \qquad \qquad X \qquad XZCO3 \qquad DMF \qquad XL:Z = COCI \qquad Y = N \text{ or } CH \qquad XLI:Z = CO \qquad XLII:Z = CO$$

[0112] Compounds such as XLVII and XLIX preferably may be prepared as outlined in Scheme 8. Dibromopyridine is combined with diaminoethane to produce amine XLIV. Treatment of amine XLIV with isatoic anhydride LV in methanol and water, followed by refluxing in formic acid affords compound XLVI. Treatment of amine XLIV with the reaction products of benzylaminodiacetic acid and acetic anhydride provides compound XLVIII. Bromopyridylamines XLVI and XLVIII are then converted to the corresponding diene anilinylamides XLVII and XLIX, respectively, by procedures analogous to those set forth in Schemes 3-7 above.

Scheme 8

[0113] Compounds such as LIV preferably may be prepared according to the synthetic route depicted in Scheme 9. Trichlorotriazine is treated with aminoindan and diisopropylethylamine to produce dichloroaminotriazine L. Treatment with bromobenzylamine and diisopropylethylamine affords diaminochlorotriazine LI. Addition of ammonia gas and dioxane provides triaminotriazine LII. Treatment with protected acrylanilide, triethylamine, POT, and dibenzylacetone palladium then yields diene anilinylamide LIII, which is deprotected with trifluoroacetic acid to provide the final product LIV.

Scheme 9

Compounds of formula (2), wherein Ar² is quinolylene and X¹ comprises -N(R⁷)-, [0114] compounds of formula (3), wherein Ar3 is quinolylene and X2 comprises -N(R9)-, and compounds of formula (4), wherein Ar⁴ is quinolylene and X³ comprises -N(R¹¹)-, preferably may be prepared according to the procedures illustrated in Scheme 10. Dihydroxyquinoline LV with dimethylaminopyridine (DMAP) in pyridine is treated with trifluoromethanesulfonic anhydride to provide bis(trifluoromethanesulfonyloxy)-quinoline LVI. Treatment of LVI with p-methoxybenzylamine affords aminoquinoline LVII. Anilinyl amides LVIII and LIX are then prepared using procedures analogous to those described for Schemes 1-9 above.

Scheme 10

- a. Tf₂O / Py / DMAP / 0 C b. p-methoxyberzylamine / 120 C c. 1,2-phenylenediamine / CO (40 psi) / Pd(OAc)₂ / dppf / DMF / DIPEA / 70 C d. 1 Butylacrylate / Pd₂(dba)₃ / POT / DMF / DIPEA / 120 C e. TFA / DCM / rT f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

[O115] Compounds of formula (3), wherein X² comprises a sulfur atom, and compounds of formula (4), wherein X³ comprises a sulfur atom, preferably may be prepared as outlined in Scheme 11. Bromide LX is converted to diaryl ester LXI using procedures analogous to those described for Scheme 6 above. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester LXI to the corresponding acid LXIV. Alternatively, ester LXI may be treated with chloroethylmorphonline, sodium iodide, potassium carbonate, triethylamine, and tetrabutylammonium iodide (TBAI) in DMF to produce ester LXIII, which is then converted to acid LXIV as in Scheme 1. Conversion of the acid LXIV to the anilinyl amide LXV is effected by procedures analogous to those set forth in Scheme 1 above.

Scheme 11

[0116] Alternatively, compounds of formula (3), wherein X² comprises a sulfur atom, and compounds of formula (4), wherein X³ comprises a sulfur atom, may be prepared according to the procedures illustrated in Scheme 12. Sulfanyl anilinylamide LXVIII is prepared using procedures analogous to those set forth in Schemes 3 and 5 above.

Scheme 12

[0117] Compounds of formula (3), wherein X^2 comprises -N(\mathbb{R}^9)-, and compounds of formula (4), wherein X^3 comprises -N(\mathbb{R}^{11})-, preferably may be prepared according to the synthetic route depicted

in Scheme 13. Amino anilinyl amide **LXXI** is prepared according to synthetic steps similar to those described for Schemes 1 and 6 above.

Scheme 13

[0118] Compounds of formula (3), wherein X² comprises a sulfur atom, and compounds of formula (4), wherein X³ comprises a sulfur atom, preferably may be prepared as outlined in Scheme 14. Phenylenediamine is reacted with di-tert-butyldicarbonate, followed by iodobenzoic acid, dimethylaminopropylethylcarbodiimide, hydroxybenzotriazole, and triethylamine to provide protected anilinyl amide LXXII. The iodide moiety of LXXII is converted to the methyl ester moiety of LXXIII using procedures analogous to those set forth for Scheme 3 above. The methyl ester moiety of LXXIII is converted to the hydroxyl moiety of LXXIV by treatment with a reducing agent such as diisobutylaluminum hydride (DIBAL-H). Addition of the heterocyclylsulfhydryl compound Het-SH with triphenylphosphine and diethylazodicarboxylate converts the hydroxyl moiety of LXXIV to the sulfanyl moiety of LXXV. LXXV is deprotected with trifluoroacetic acid to afford the sulfanyl anilinyl amide LXXVI.

[0119] Compounds of formula (3), wherein X² is a chemical bond, preferably may be prepared according to the synthetic route depicted in Scheme 15. Thus, chloroarylanilinylamide **LXXVII** is treated with aryl boronic acid, benzene, ethanol, aqueous sodium carbonate, and triphenylphosphine palladium to afford the diarylanilinylamide **LXXVIII**.

Scheme 15

[0120] Compounds such as LXXXI preferably may be prepared according to the procedues illustrated in Scheme 16. Thus, benzene-1,2-carbaldehyde LXXIX in acetic acid is treated with paminomethylbenzoic acid to produce the benzoic acid LXXX. The acid LXXX is converted to the corresponding anilinylamide LXXXI by treatment with hydroxybenzotriazole, ethylenedichloride, and phenylenediamine.

Scheme 16

a. p-aminomethylbenzoic acid/AcOH/5 min/reflux
 b. HOBT/EDC/1,2-diamino benzene

[0121] Compounds such as LXXXVI and LXXXIX preferably may be prepared according to the procedures illustrated in Scheme 18. Phthalic anhydride LXXXV and p-aminomethylbenzoic acid are combined in acetic acid to produce an intermediate carboxylic acid, which is converted to the anilinylamide LXXXVI using procedures analogous to those set forth in Schemes 15 and 16 above.

[0122] The addition of 4-(2-aminoethyl)phenol to phthalic anhydride LXXXV in acetic acid affords the hydroxyl compound LXXXVII. The hydroxyl group of LXXXVIII is converted to the triflate group of LXXXVIII by treatment with sodium hydride, THF, DMF, and phenylaminoditriflate. Treatment of LXXXVIII according to procedures analogous to those described for Scheme 3 above affords the anilinylamide LXXXIX.

Scheme 18

- a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
- b. HOBT/EDC/1,2-diamino benzene
- c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
- d. PhNTf₂/NaH/THF-DMF/30 min/0°C
- e. 1. CO/Pd(OAc)₂/dppf/Et₃N/MeOH-DMF/4 days/75°C
- 2. AcOH/HCI/3 hrs/reflux

[0123] Compounds such as XCI-XCVI preferably may be prepared according to the synthetic route depicted in Scheme 19. Treatment of isatoic anhydride XC with p-aminomethylbenzoic acid in water and triethylamine, followed by formic acid affords an intermediate carboxylic acid, which is converted to anilinylamide XCI using procedures analogous to those described for Scheme 16 above.

[0124] Alternatively, treatment of isatoic acid XC with p-aminomethylbenzoic acid in water and triethylamine, follwed by hydrochloric acid and sodium nitrite affords an intermediate carboxylic acid, which is converted to anilinylamide XCII using procedures analogous to those described for Scheme 16 above.

[0125] Alternatively, treatment of isatoic acid XC with p-aminomethylbenzoic acid in water and triethylamine affords benzoic acid XCIII. Treatment of XCIII with sodium hydroxide, dioxane, methylchloroformate, and methanol affords an intermediate quinazolinedione carboxylic acid, the acid moiety of which is then converted to the anilinylamide moiety of XCIV using procedures analogous to those described for Scheme 16 above. Alternatively, the intermediate quanzolinedione carboxylic acid in DMF is treated with potassium carbonate and methyl iodide to produce an intermediate benzoic acid methyl ester, which is converted to an intermediate benzoic acid by treatment with

sodium hydroxide, methanol, and water. The benzoic acid is then converted to the corresponding anilinylamide **XCV** using procedures analogous to those described for Scheme 16 above.

[0126] Alternatively, treatment of XCIII with acetic anhydride followed by acetic acid produces an intermediate carboxylic acid, which is converted to anilinylamide XCVI using procedures analogous to those described for Scheme 16 above.

[0127] Compounds such as **C** preferably may be prepared as outlined in Scheme 20.

Alkylamine **XCVII** is treated with thiocarbonyl diimidazole in dichloromethane, follwed by ammonium hydroxide to afford thiourea **XCVIII**. Treatment of thiourea **XCVIII** with methylmethoxyacrylate in dioxane and N-bromosuccinimide produces thiazole ester **IC**. The ester **IC** is converted to the corresponding anilinylamine **C** using procedures analogous to those set forth in Scheme 1 above.

Scheme 20

[0128] Compounds of formula (3), wherein X² is a chemical bond and Cy³ has an amino substituent preferably may be prepared according to the synthetic route depicted in Scheme 21. Thus, protected iodoarylanilinylamide Cl is treated according to procedures analogous to those described for Scheme 15 above afford the diarylanilinylamide Cll. The aldehyde moiety in Cll is converted to the corresponding secondary amine moiety by treatment with the primary amine and sodium triacetoxyborohydride followed by glacial acetic acid. The resultant compound is deprotected to yield Clll using procedures analogous to those set forth in Scheme 3 above.

Scheme 21

[0129] Compounds of formula (3), wherein X² comprises an alkynylene moiety, and compounds of formula (4), wherein X³ comprises an alkynylene moiety, preferably may be prepared as outlined in Scheme 22. Treatment of protected iodoarylanilinylamide CI with triphenylphosphine palladium chloride, cuprous iodide, and 1-ethynylcyclohexylamine affords the alkynylarylanilinylamide CIV. The primary amine moiety in CIV is converted to the corresponding secondary amine and the aniline moiety is deprotected to afford CV using procedures analogous to those described for Scheme 21 above.

Scheme 22

Scheme 24

[0130] Compounds such as **CVIII** preferably may be prepared according to the synthetic route depicted in Scheme 24. Dichloroaminotriazine **CVI** is treated with methyl-4-aminobenzoate in the presence of diisopropylethylamine to produce diaminotriazine **CVII**. Addition of ammonia gas and dioxane, followed by a saponification and a peptide coupling using the same procedures analogous to those described for Scheme 1 above.

Scheme 30

[0131] Compounds such as CX preferably may be prepared according to the synthetic route depicted in Scheme 30. The Grignard reaction of trichloroaminotriazine with various alkyl magnesium bromide, followed by a treatment with methyl-4-aminobenzoate in the presence of diisopropylethylamine yields alkylaminotriazine CIX. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester CIX to the corresponding anilinyl amide CX.

Scheme 32

[O132] Amination of dichlorotriazine proceeded using the usual condition described in Scheme 1 to afford CXI. Stille coupling using vinyl stannane provides CXII. Treatment with protected iodoanilide, triethylamine, POT and dibenzylacetone palladium then yields anilinylamide, which is deprotected with trifluoroacetic acid to provide the alkene CXIII. Hydrogenation of the alkene affords the final compound CXIV.

Scheme 33

[O133] Compounds such as CXVIII preferably may be prepared according to the synthetic route depicted in Scheme 33. Treatment of methoxyaminobenzothiazole with tribromide boron affords the corresponding acid CXV. Mitsunobu reaction using hydroxyethyl morpholine in the presence of diethylazodicarboxylate and triphenylphosphine yields the amine CXVI. Reductive amination with methyl-4-formylbenzoate using phenylsilane and tin catalyst yields to the ester CXVII. Saponification followed by the usual peptide coupling analogous to those describe for Scheme 1 above provides the desired anilide CXVIII.

Scheme 42

[0134] Treatment 4-methylcyanobenzoic acid with hydrogen sulfide affords **CXIX**, which is subjected to cyclization in the presence of 1,3-dichloroacetone to yield **CXX**. Treatment with morpholine followed by a peptide coupling using the standard condition produces **CXXI**.

Scheme 49

[0135] Compounds such as CXXIII and CXXVII preferably may be prepared according to the synthetic scheme 49. Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and phenyl hydrazine followed by saponification, afforded the intermediate acid CXXII. This material was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXIII.

[O136] Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and a 1:1 mixture AcOHHCI (conc.) afforded the intermediate acid CXXIV. This keto-acid reacting with sulfur and malonodinitrile in the presence of a base, produced the thiophene CXXV, which was converted into the desired CXXVII using standard procedures.

Scheme 50

[0137] Compounds such as CXXX preferably may be prepared according to the synthetic scheme 50. Treatment of 4-cyanomethylbenzoic acid with hydroxylamine produced the amidoxime CXXVIII, which upon treatment with acetic anhydride was converted into the oxadiazole CXXIX. The latter was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXX.

OHC COOH 1. SOCI₂, DMF, DCM 2. H₂N NHtBoc DIPEA 1. CHCl₃/THF 1. CHCl₃/THF NHtBoc NCO MeS NHTBOC CXXXII Addimethoxyaniline CXXXIII NHtBoc CXXXIII

[0138] Compounds such as CXXXIII preferably may be prepared according to the synthetic route depicted in Scheme 57. Treatment of 4-formylbenzoic acid with thionyl chloride afford the acyl

chloride which is coupled with protected anilide to produce CXXXI. Reductive amination with dimethoxyaniline using phenylsilane and tin catalyst yields to the protected anilide CXXXII. Treatment with isocyanate followed by deprotection with trifluoroacetic acid provides the ureidoanilide CXXXIII.

Pharmaceutical Compositions

[0139] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0140] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0141] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate,

or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

[0142] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

Inhibition of Histone Deacetylase

[0143] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study of the role of histone deacetylase in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

[0144] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., 265: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton et al., Science, 272: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0145] In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC

4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.

[0146] Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0147] Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

[0148] The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell; a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

[0150] In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0151] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

[0152] It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0153] The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0154] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0155] When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about $0.01~\mu\text{M}$ to about $100~\mu\text{M}$, more preferably from about $0.05~\mu\text{M}$ to about $50~\mu\text{M}$, still more preferably from about $0.1~\mu\text{M}$ to about $25~\mu\text{M}$, and still yet more preferably from about $0.5~\mu\text{M}$ to about $25~\mu\text{M}$. For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0156] In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and/or HDAC-8 (see e.g., GenBank Accession Number U50079)

for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0157] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

[0158] For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

[0159] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0160] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos.

5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0161] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

[0162] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

[0163] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) Methods in Molec. Biol. 20: 465-496).

[0164] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table 1.

Table 1

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene
HDAC1 AS1 HDAC1 AS2	Human HDAC1 Human HDAC1	U50079	1585-1604 1565-1584	5'GAAACGTGAGGGACTCAGCA-3'	3:UTR 3:UTR
HDAC1 MM	Human HDAC1	050079	1585-1604	5'-GTTAGGTGAGGCACTGAGGA-3'	3'-UTR
HDAC2 AS	Human HDAC2	U31814	1643-1622	5'GCTGAGCTGTTCTGATTTGG-3'	3'-UTR
HDACZ MM	Human HDAC2	U31814	1643-1622	5'-CGTGAGCACTTCTCATTTCC-3'	3'UTR
HDAC3 AS	Human HDAC3	AF039703	1276-1295	5'-CGCTTTCCTTGTCATTGACA-3'	3'UTR
HDAC3 MM	Human HDAC3	AF039703	1276-1295	5'-GCCTTTCCTACTCATTGTGT-3'	3'-UTR
HDAC4 AS1	Human HDAC4	AB006626	514-33	5-GCTGCCTGCCGTGCCCACCC-3'	5'UTR
HDAC4 MM1	Human HDAC4	AB006626	514-33	5'-CGTGCCTGCGCTGCCCACGG-3'	5'-UTR
HDAC4 AS2	Human HDAC4	AB006626	7710-29	5'-TACAGTCCATGCAACCTCCA-3'	3'-UTR
HDAC4 MM4	Human HDAC4	AB006626	7710-29	5'ATCAGTCCAACCAACCTCGT-3'	3'-UTR
HDAC5 AS	Human HDAC5	AF039691	2663-2682	5'-CTTCGGTCTCACCTGCTTGG-3'	3'-UTR
HDAC6 AS	Human HDAC6	AJ011972	3791-3810	5'-CAGGCTGGAATGAGCTACAG-3'	3'-UTR
HDAC6 MM	Human HDAC6	AJ011972	3791-3810	5'-GACGCTGCAATCAGGTAGAC-3'	3'UTR
HDAC7 AS	Human HDAC7	AF239243	2896-2915	5'-CTTCAGCCAGGATGCCCACA-3'	3'-UTR
HDAC8 AS1	Human HDAC8	AF230097	51-70	5'-CTCCGGCTCCTCCATCTTCC-3'	5'-UTR
HDAC8 AS2	Human HDAC8	AF230097	1328-1347	5'AGCCAGCTGCCACTTGATGC-3'	3'-UTR

[0165] The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

EXAMPLES

Pathway A NH₃ gas 1,4-dioxane sealed flask 70°C
$$R^1R^2NH$$
 R^1R^2NH R^1

Example 1

4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (compound 8)

Step 1: Methyl-4-[(4,6-dichloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 3) [O166] To a stirred solution at -78° C of cyanuric chloride 1 (8.23 g, 44.63 mmol) in anhydrous THF (100 mL) under nitrogen was added a suspension of methyl 4-(aminomethyl)benzoate.HCl 2 (10.00 g, 49.59 mmol), in anhydrous THF (50 mL), followed by i-Pr₂NEt (19.00 mL, 109.10 mmol). After 30 min, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 5/95) to afford the title compound 3 (12.12 g, 38.70 mmol, 87% yield) as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): AB system (δ _A = 8.04, δ _B = 7.38, J = 8.5 Hz, 4H), 6.54 (bt, 1H), 4.76 (d, J = 6.3 Hz, 2H), 3.93 (s, 3H).

Pathway A

Step 2: Methyl-4-[(4-amino-6-chloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 4) [O167] In a 150 mL sealed flask, a solution of 3 (6.00 g, 19.16 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH₃ gas for 5 min, and warmed to 70°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH₃ gas was repeated at room temperature for 5 min, and the reaction mixture was warmed to 70°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 30/70) to afford the title compound 4 (5.16 g, 17.57 mmol, 91% yield) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): AB system (δ_A = 8.01, δ_B = 7.35, J = 8.1 Hz, 4H), 5.79 (bs, 1H), 5.40-5.20 (m, 2H), 4.72-4.63 (m, 2H), 3.91 (s, 3H).

Pathway B

Step 2: Methyl 4-I(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 5) [0168] To a stirred solution at room temperature of 3 (3.00 g, 9.58 mmol) in anhydrous THF (50 mL) under nitrogen were added iPr₂NEt (8.34 mL, 47.90 mmol) and 2-aminoindan.HCl (1.95 g, 11.50 mmol) or R¹R²NH (1.2 equiv), respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated to afford the title compound 5 (4.06 g, 9.91 mmol, quantitative yield) as a white powder. 1 H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 8.06-7.94 (m, 2H), 7.43-7.28 (m, 2H), 7.24-7.12 (m, 4H), 6.41 and 6.05 (2 bt, 1H), 5.68-5.44 (m, 1H), 4.92-4.54 (m, 3H), 3.92 (bs, 3H), 3.41-3.12 (m, 2H), 2.90-2.70 (m, 2H).

Step 3: Methyl-4-[(4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 6)
General procedure for the amination with NH₃ gas:

[0169] In a 150 mL sealed flask, a solution of **5** (3.90 g, 9.51 mmol) in anhydrous 1,4-dioxane (80 mL) was stirred at room temperature, saturated with NH₃ gas for 5 min, and warmed to 140°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH₃ gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 3/97) to afford the title compound **6** (3.50 g, 8.96 mmol, 94% yield) as a pale yellow sticky solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.99 (bd, J = 8.2 Hz, 2H), 7.41-7.33 (m, 2H), 7.24-7.13 (m, 4H), 5.50-5.00 (m, 2H), 4.90-4.55 (m, 5H), 3.92 (s, 3H), 3.40-3.10 (m, 2H), 2.90-2.70 (m, 2H). ¹³C NMR: (75 MHz, CDCl₃) δ (ppm): 166.88, 167.35, 166.07, 144.77, 141.07, 129.82, 128.93, 127.01, 126.61, 124.70, 52.06, 51.80, 44.25, 40.16. HRMS (calc.): 390.1804, (found): 390.1800.

Pathways A and B, step 3, general procedure with primary and/or secondary amines:

[0170] In a 50-75 mL sealed flask, a stirred solution of 4 (500 mg, 1.70 mmol, 1 equiv), iPr_2NEt (1.48 mL, 8.51 mmol, 5 equiv) and R^1R^2NH or R^3R^4NH (1.5-3 equiv) in anhydrous THF or 1,4-dioxane (20-30 mL) was warmed to 120-140°C for 15-24 h. Then, the reaction mixture was allowed to cool

to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel to afford the title compound.

Step 4: 4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (compound 7) [0171] To a stirred solution at room temperature of 6 (2.07 g, 5.30mmol) in THF (50 mL) was added a solution of LiOH.H₂O (334 mg, 7.96 mmol) in water (25 mL). After 18 h, the reaction mixture was diluted in water and acidified with 1 N HCl until pH 5-6 in order to get a white precipitate. After 1 h, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 7 (1.73 g, 4.60 mmol, 87% yield) as a white solid. 1 H NMR (300 MHz, acetone-d₆) δ (ppm): 8.05 (bd, J = 8.1 Hz, 2H), 7.56-7.42 (m, 2H), 7.30-7.10 (m, 4H), 5.90-5.65 (m, 2H), 4.85-4.60 (m, 4H), 3.40-2.80 (m, 4H). HRMS (calc.): 376.1648, (found): 376.1651.

Step 5: 4-{[4-Amino-6-{2-indanyl-amino}-[1,3,5]-triazin-2-yl-amino]-methyl}-N-{2-amino-phenyl}-benzamide (compound 8)

[0172] To a stirred solution at room temperature of **7** (200 mg, 0.53 mmol) in anhydrous DMF (5 mL) under nitrogen were added Et₃N (74 μ l, 0.53 mmol) and BOP reagent (282 mg, 0.64 mmol), respectively. After 40 min, a solution of 1,2-phenylenediamine (64 mg, 0.58 mmol), Et₃N (222 μ l, 1.59 mmol) in anhydrous DMF (2 mL) was added dropwise. After 1.5 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 2/98 \rightarrow 5/95) to afford the title compound **8** (155 mg, 0.33 mmol, 63% yield) as a pale yellow foam. ¹H NMR (300 MHz, acetone-d₆) δ (ppm): 9.04 (bs, 1H), 7.96 (bd, J = 8.0 Hz, 2H), 7.50-7.40 (m, 2H), 7.30 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.22-7.08 (m, 4H), 6.99 (ddd, J = 8.0 Hz, 7.5 Hz, 1.5 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.5 Hz, 1.4 Hz, 1H), 6.60-5.49 (m, 4H), 4.80-4.50 (m, 4H), 3.30-3.08 (m, 2H), 2.96-2.74 (m, 2H).

EXAMPLES 2-28

[0173] Examples 2 to 28 describe the preparation of compounds 9 to 35 using the same procedure as described for compound 8 of Example 1. Characterization data are presented in Tables 2a and 2b.

lable Za
Characterization of Compounds Prepared in Examples 2-28

Cpd Y	\		×	Name	Characterization	Schm
4-11,3,5-triazin-2-	4-[(4-amino-4-4-4-11,3,5]-t	4-[(4-amino-	4-[(4-amino-{ 4-yl-[1,3,5]-t	olin-	¹ H NMR (CDCl ₃) 8 (ppm): 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.31 (m, 1H), 7.08 (dt,	
9 C NH2 NH2 Jamino-methyl]-N42-			ylamino}-me	thyl]-N42-	J = 7.6 Hz, 1.5 Hz, 1H), 6.82 (t, J = 6.7 Hz, 2H), 5.62 (t,	1A
amino-pheny!)-	amino-pheny amino-pheny	amino-pheny	amino-pheny	- -	J = 5.9 Hz, $J = 1.90 (bs, 2H)$, $J = 6.0 Hz, 2H)$,	
benzamide	benzamide	benzamide	benzamide		3.75-3.62 (m, 10H).	
					¹ H NMR (acetone-d ₆) 8 (ppm): 9.07 (bs, 1H), 8.05-7.95	
4-[[4-amin	4-([4-amin	4-([4-amin	4-([4-amin	4-([4-amino-6-(1-indanyl-	(m, 2H), 7.55-7.45 (m, 2H), 7.37-7.10 (m, 5H), 7.04 (dt, J	
amino}-[1,	amino)-[1,	amino}-[1,	amino)-[1,	amino)-[1,3,5]-triazin-2-	= 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H),	
10 NH2 ylamino]-r			ylamino]+n	ylamino]-methyl}-N4(2-	6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.55 (m, 5H),	IA
HN- amino-phenyl)-	HN- amino-phe	amino-phe	amino-phe	enyl)-	4.75-4.60 (m, 3H), 3.05-2.75 (m, 2H), 2.60-2.45 (m, 1H)	_
benzamide	benzamic	benzamic	benzamic	<u>e</u>), 2.00-1.84 (m, 1H). HRMS (calc.): 466.2229, (found):	
					466.2225	
					1H NMR (acetone-de) 8 (ppm): mixture of rotamers,	
					9.05-9.00 (m, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.93 (s),	
N(2-Amir	N(2-Amir	M2-Amir	M2-Amir	N(2-Amino-phenyl)-4-{[4-	7.84 (d, J = 8.0 Hz), 7.72 (d, J = 8.2 Hz), 7.58-7.40 (m,	
- amino-64	amino-64	amino-64	amino-64	amino-6-(4-phenyl-	3H), 7.31-7.19 (m, 3H), 7.12-7.05 (m), 6.98 (d, J = 8.1	
11 NH2 piperazin-1-yl			piperazin	-1-y()-	Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.80 (t, J = 7.1 Hz,	1A
[1,3,5]tria	\(\)	[1,3,5]tria	[1,3,5]tria	[1,3,5]triazin-2-ylamino]-	1H), 6.67 (t, J = 7.7 Hz, 1H), 6.57-6.50 (m, 1H), 5.78-	
methyl}&	methy!}-	methy } -	methy }-b	methy!}-benzamide	5.60 (m, 2H), 4.674.64 (m, 2H), 3.88-3.84 (m, 4H), 3.14	-
					(s, 4H). HRMS (calc.): 477.2389 [M ⁺ · – NH ₄], (found):	
					477.2383	

Schm	1A	18	18	1A	1A
Characterization	¹ H NMR (acetone-d ₆) 8 (ppm): 9.08 (bs, 1H), 8.51 (bs, 1H), 8.05-7.90 (m, 2H), 7.80-7.60 (m, 1H), 7.55-7.15 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85-6.55 (m, 1H), 5.84 (bs, 2H), 4.75-4.60 (m, 4H). HRMS (calc.): 441.2025, (found): 441.2029	¹ H NMR (acetone-d ₆) 8 (ppm): 9.08 (bs, 1H), 8.05-7.95 (m, 2H), 7.56-7.44 (m, 2H), 7.34 (bd, J = 7.7 Hz, 1H), 7.27-7.10 (m, 8H), 7.04 (td, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.55-5.90 (m, 3H), 4.90-4.58 (m, 6H), 3.40-2.80 (m, 4H). HRMS (calc.): 582.2855, (found): 582.2838	¹ H NMR (acetone-d ₆) 5 (ppm): 9.05-9.00 (m, 1H), 8.03-7.87 (m, 2H), 7.80-7.70 (m, 2H), 7.63-7.20 (m, 9H), 7.00 (t, 1H), 6.86 (d, 1H), 6.66 (t, 1H), 6.50-5.50 (m, 6H), 4.75-4.55 (m, 3H). HRMS (calc.): 514.2229, (found): 514.2232	¹ H NMR (CDCl ₃) & (ppm): 7.96 (bs, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.08 (dt, J = 7.7 Hz, 1.4 Hz, 1H), 6.83 (t, J = 6.6 Hz, 2H), 5.47 (bs, 1H), 4.80 (bs, 2H), 4.60 (d, J = 6.0 Hz, 2H), 3.88 (bs, 2H), 3.67 (t, J = 5.2 Hz, 4H), 1.66-1.58 (m, 2H), 1.56-1.48 (m, 4H).	¹ H NMR (CDCI ₃) & (ppm): 7.97 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.39-7.34 (m, 3H), 7.10 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85 (t, J = 7.0 Hz, 2H), 5.56 (bs, 1H), 4.90 (bs, 3H), 4.62 (s, 2H), 4.25-4.19 (m, 1H) 3.88 (bs, 2H), 1.95 (m, 2H), 1.71-1.59 (m, 4H), 1.43-1.37 (m, 2H).
Name	4-{I4-amino-6-(2- pyridinyl-methyl-amino}- [1,3,5]-triazin-2- ylamino}-methyl}-N-(2- amino-phenyl)- benzamide	4-{[4,6-bis-{2-indanyl-amino}-[1,3,5]-triazin-2-ylamino}-methyl}-N-{2-amino-phenyl}-benzamide	4-{[4-Amino-6-(91+ fluoren-9-ylamino}- [1,3,5]triazin-2-ylamino}- methyl}-N-(2-amino- phenyl}-benzamide	N-(2-amino-phenyl)-4-[(4-amino-6-piperidin-1-yl-[1,3,5]-triazin-2-ylamino)-methyl]-benzamide	4-[(4-amino-6- cyclopentyl-amino- [1,3,5]-triazin-2-yl- amino) -methyl]-N4(2- amino-phenyl)- benzamide
×	NH. 2	TZ -	NH ₂	NH ₂	NH ₂
λ	ZI	HN	HN -	Z	± ±
Cpd	12	13	14	15	16
Ex.	5	9	7	8	6

\vdash	Y	X	Name	Characterization	Schm
H ₃ O _E H	CH ₃	Å.	(1R)-4-{[4-amino-6-{2-exo-fenchyl-amino}-[1,3,5]-triazin-2-ylamino]-methyl}-N-{2-amino-phenyl}-benzamide	¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), AB system ($\delta_A = 8.00$, $\delta_B = 7.51$, $J = 8.0$ Hz, 4H), 7.33 (bd, $J = 7.7$ Hz, 1H), 7.03 (ddd, $J = 8.0$ Hz, 7.3 Hz, 1.4 Hz, 1H), 6.90 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H), 6.71 (dt, $J = 7.6$ Hz, 1.4 Hz, 1H), 6.90 (dd, $J = 8.0$ Hz, $I.4$ Hz, $I.4$), $I.80$ -5.20 (m, 3H), 4.67 (bs, 4H), 3.87 (bd, $J = 9.1$ Hz, 1H), 1.80 -1.60 (m, 4H), 1.56 -1.42 (m, 1H), 1.34 -1.00 (m including 2 s, 8H), 0.84 (s, 3H). HRMS (calc.): 486.2855 . (found): 486.2844	14
	NH NH	TX.	4-{[4-allyl-amino-6-{2-indanyl-amino}-{1,3,5]-triazin-2-ylamino}-methyl}-N-{2-amino-phenyl}-benzamide	¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.4 Hz, 2H), 7.58-7.42 (m, 2H), 7.34 (bd, J = 8.0 Hz, 1H), 7.27-7.10 (m, 4H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-5.70 (m, 3H), 5.26-5.00 (m, 2H), 4.86-4.54 (m, 4H), 4.10-3.90 (m, 2H), 3.38-3.10 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 506.2542, (found): 506.2533	18
<u>_</u> >		₹ ¥	4-[[4-cyclopropyl-amino-6{2-indanyl-amino}-[1,3,5]-triazin-2-ylamino]-methyl]-N{2-amino-phenyl}-benzamide	¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.7 Hz, 2H), 7.60-7.40 (m, 2H), 7.33 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.28-7.10 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.3 Hz, 1H), 6.67-5.80 (m, 2H), 4.90-4.50 (m, 4H), 3.40-3.10 (m, 2H), 3.05-2.70 (m, 3H), 0.75-0.43 (m, 4H). HRMS (calc.): 506.2542, (found): 506.2548	18
\ <u>_</u> /	ZI	NH ₂	4-[(4-Amino-6- phenethylamino- [1,3,5]triazin-2-ylamino)- methyl]-N42-amino- phenyl}-benzamide	¹ H NMR (acetone-d ₆) δ (ppm): 9.03 (s, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.99 (td, J = 8.0 Hz, 1.3 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.3 Hz, 1.1), 6.86 (dd, J = 8.0 Hz, 1.3 Hz, 1.4 Hz, 1.1), 6.62-5.40 (m, 5H), 4.75-4.45 (m, 3H), 3.59-3.45 (m, 2H), 2.95-2.70 (m, 2H). HRMS (calc.): 454.2229, (found): 454.2235	1A

Schm	18	18	1A	1A	18
Characterization	¹ H NMR (CDCl ₃ /MeOD) δ (ppm): 7.72 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 1H), 6.91 (td, J = 7.7 Hz, 1.2 Hz, 1H), 6.70-6.61 (m, 4H), 4.61 (bs, 2H), 3.58-3.52 (m, 9H).	¹ H NMR (CDCl ₃ /MeOD) δ (ppm): 8.06 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.02-6.96 (m, 2H), 6.84-6.71 (m, 3H), 4.61 (bs, 2H), 4.03 (t, J = 8.5 Hz, 2H), 3.02 (t, J = 8.5 Hz, 2H).	¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.06 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.21-6.70 (m, 6H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-5.70 (m, 5H), 4.75-4.55 (m, 3H), 3.81 (s, 3H), 3.55-3.45 (m, 2H), 2.90-2.78 (m, 2H). HRMS (calc.): 484.2335, (found): 484.2331	¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.03 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.38-7.17 (m, 2H), 7.17-6.95 (m, 4H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (t, J = 7.0 Hz, 1H), 6.50-5.60 (m, 5H), 4.75-4.55 (m, 3H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H). HRMS (calc.): 472.2135, (found): 472.2146	¹ H NMR (acetone-d ₆) δ (ppm): 9.06 (bs, 1H), 8.04-7.93 (m, 2H), 7.57-7.12 (m, 12H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.72 (bt, J = 7.6 Hz, 1H), 6.68-5.90 (m, 3H), 4.84-4.50 (m, 7H), 3.35-3.13 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 556.2699, (found): 556.2706
Name	N{2-Amino-phenyl}-4-[[4-amino-6-(3,4,5-trimethoxy-phenylamino]-[1,3,5]triazin-2-ylamino]-methyl}-benzamide	4-[[4-Amino-6-(2,3-dihydro-indol-1-yl)-[1,3,5]triazin-2-ylamino]-methyl}-N-(2-amino-phenyl)-benzamide	4-(14-Amino-6-[2-(2-methoxy-phenyl)-ethylamino]-[1,3,5]triazin-2-ylamino}-methyl)-N-(2-amino-phenyl)-benzamide	4-{{4-Amino-6-{2-{2- fluoro-phenyl}- ethylamino}- [1,3,5]triazin-2- ylamino}-methyl}-N-{2- amino-phenyl}- benzamide	4-[[4-benzyl-amino-6-(2-indanyl-amino]-[1,3,5]-triazin-2-ylamino]-methyl}-N-(2-amino-phenyl}-benzamide
×	NH ²	NH ₂	NH ₂	NH ₂	ŽTI.
Ϋ́	MeO H	\(\rac{z}{} \)	OMe	NH NH	TN TN
Cpd	.21	22	23	24	25
Ex.	14	15	16	17	18

Schm	 	18	14	1A	18
Characterization	¹ H NMR: (CDCl ₃) & (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz, 8H), 1.631.53 (m, 12H).	¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.05-7.90 (m, 2H), 7.60-7.40 (m, 2H), 7.35-7.05 (m, 10H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.60-5.70 (m, 3H), 4.95-4.50 (m, 5H), 3.70-2.80 (m, 8H), HRMS (calc.): 552.2750 [M ⁺ − NH ₄], (found): 552.2746	¹ H NMR (CDCl ₃) 8 (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz), 1.63-1.53 (m, 12H).	¹ H NMR (acetone-d ₆) & (ppm): 9.04 (s, 11H), 7.95 (d, J = 7.3 Hz, 2H), 7.45 (d, J = 7.1 Hz, 2H), 7.38-7.15 (m, 6H), 7.00 (td, J = 8.0 Hz, 1.5 Hz, 11H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 11H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 11H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 11H), 6.67 (25 (m, 3H), 5.85-5.55 (m, 3H), 4.61 (d, J = 6.3 Hz, 2H), 4.54 (d, J = 5.2 Hz, 2H). HRMS (calc.): 440.2073, (found): 440.2078	¹ H NMR (acetone-d ₆) 5 (ppm): mixture of rotamers, 9.20-9.00 (m, 1H), 8.70-8.35 (m, 2H), 8.05-7.90 (m, 2H), 7.85-7.55 (m, 1H), 7.55-7.10 (m, 8H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (bd, J = 7.4 Hz, 1H), 6.71 (bt, J = 7.3 Hz, 1H), 6.80-6.00 (m, 3H), 4.84-4.50 (m, 7H), 3.34-3.12 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.):
Name	N(2-Amino-phenyl)-4- [(4,6-di-piperidin-1-yl- [1,3,5]triazin-2-ylamino)- methyl]-benzamide	4-{[6-(2-indanyl-amino}- 4-phenethyl-amino- [1,3,5]-triazin-2- ylamino]-methyl}-N-(2- amino-phenyl)- benzamide	4-{{4-benzyl-amino-6-{2-indanyl-amino}-{1,3,5}-triazin-2-ylamino}-methyl}-N-{2-amino-phenyl}-benzamide	4-[(4-Amino-6- benzylamino- [1,3,5]triazin-2-ylamino)- methyl]-N-(2-amino- phenyl)-benzamide	4-[[6-(2-indanyl-amino)-4-(3-pyridinyl-methyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl]-N-(2-amino-phenyl)-
×		IZ	NH ₂	Ϋ́	ZI
>		HN		ZI	- F
pdS	26	27	28	59	30
EX.	19	20	21	22	.:

Schm	18	18	18	18	IA
Characterization	¹ H NMR (CDCl ₃) δ (ppm): 7.89 (bs, 1H,), 7.82 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.09 (dt, J = 7.7 Hz, 1.6 Hz, 1H), 6.87-6.82 (m, 2H), 4.83 (bs, 1H), 4.62 (d, J = 6.0 Hz, 2H), 4.24 (m, 1H), 3.88 (bs, 1H), 2.04-1.96 (m, 2H), 1.70-1.52 (m, 10H), 1.46-1.38 (m, 2H).	¹ H NMR (CDCl ₃) & (ppm): 8.27 (bs, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.29 (m, 3H), 7.05 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.81-6.76 (m, 2H), 5.62 (bs, 2H), 4.57 (bs, 2H), 3.91 (bs, 2H), 3.69 (m, 4H), 3.45 (m, 2H), 2.57 (t, J = 6.2 Hz, 2H), 2.47 (m, 4H), 1.71 (m, 4H), 1.59-1.50 (m, 6H).	¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.08-7.95 (m, 2H), 7.60-7.43 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.55-6.05 (m, 2H), 4.86-4.60 (m, 5H), 3.80-3.56 (m, 8H), 3.38-3.12 (m, 2H), 3.04-2.82 (m, 2H).	¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), 8.01 (bd, J = 7.4 Hz, 2H), 7.56-7.43 (m, 2H), 7.33 (bd, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.75 (m, 2H), 4.90-4.58 (m, 5H), 3.66-2.34 (m, 16H).	¹ H NMR (acetone-d ₆) 8 (ppm): 10.00 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.70-7.50 (m, 1H), 7.50-7.22 (m, 4H), 7.18-6.91 (m, 4H), 6.85 (d, J = 7.1 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.40-5.90 (m, 3H), 4.75-4.50 (m, 2H), 4.37 (s, 2H), 3.62 (d, J = 6.3 Hz, 2H), 2.99 (s, 2H).
Name	N{2-Amino-phenyl}-4-[(4- piperidin-1-yl-6- pyrrolidin-1-yl- [1,3,5]triazin-2-ylamino}- methyl]-benzamide	N42-Amino-phenyl)-4-[[2- piperidin-1-yl-6-(2- pyrrolidin-1-yl- ethylamino)-pyrimidin-4- ylamino]-methyl}- benzamide	4-{[6-{2-indanyl-amino}- 4-morpholin-4-yl-[1,3,5]- triazin-2-ylamino}- methyl}-N{2-amino- phenyl}-benzamide	N4(2-Amino-phenyl)-4-[[2- piperidin-1-yl-6-(2- pyrrolidin-1-yl- ethylamino)-pyrimidin-4- ylamino]-methyl}- benzamide	4{{4-Amino-6-[2-{1} H indol-3-yl}-ethylamino]-[1,3,5]triazin-2-ylamino}-methyl}-N{2-amino-phenyl}-benzamide
×	Į.	IZ Z	Z-\ O	Z-\ _O	NH ₂
γ	Ž	رً ا	HN	HN—	NT NT
Cpd	31	32	33	34	35
Ex.	24	25	26	27	28

	<u> </u>
2 p	
Table 2b	_ \>
	Z= Z= >≺ ZI
	ž-(

Γ-			Г	
Schm	IA	18	18	18
Characterization	4-[[4-amino-6-(3-phenyl-1H), 7.96 (d, J=8.2 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H), 7.35-7.10 (m, 6H), 7.00 (t, J=7.7 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.67 (t, J=7.7 Hz, 1H), 6.60-5.40 (m, 6H), 4.62 (s, 2H), 3.35 (dd, J=12.1, 6.9 Hz, 2H), phenyll-benzamide 2.75-2.60 (m, 2H), 1.95-1.80 (m, 2H).		¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.06 (bs, 1H), 8.00 (bd, J = 7.1, 2H), 7.50 (bs, 1H), 7.33 (d, J = 6.6 Hz, 1H), 7.28-7.07 (m, 4H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.55-5.70 (m, 3H), 4.904.50 (m, 5H), 3.40-2.80 (m, 6H), 1.07 (bs, 1H), 0.44 (bs, 2H), 0.23 (bs, 2H).	N(2-amino-phenyl) 4-{(4-7.83 (d, J = 6.6 Hz, 2H); 7.45-7.05 (m, 8H), 7.08 (td, rbutyl-amino-6-1.3, 5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.3,5]triazin-2-yl-amino-1.4,5 (m, 2H), 2.40-2.25 (m, 2H), 1.60-1.45 (m, 2H), 1.60-1.
Name	4-{[4-amino-6-(3-phenyl-propyl-1-amino}-[1,3,5]triazin-2-yl-amino]-methyl}-W(2-amino-phenyl}-benzamide	N-(2-amino-phenyl)-4-[(4-cyclopropyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl-benzamide	N-(2-amino-phenyl)-4-[(4- cyclopropyl- methylamino-6-(2- indanyl-amino)-[1,3,5]- triazin-2-yl-amino]- methyl}-benzamide	M(2-amino-phenyl)-4-[(4- n-butyl-amino-6- phenethyl-amino- [1,3,5]triazin-2-yl-amino)- methyl]-benzamide
\	NH ₂	¥ /	IZ	n-BuNH
×	ŽI	ZI	HN-	
Pd C	470	471	472	473
Ĕ	329	330	331	332

8

4-{[4-	N(2-amino-phenyl)-4-[[4-	4-([4-	Characterization NMR (300 MHz, acetone-d ₆) & (ppm): 9.02 (s), 88 (s), 8.40 (dd, J = 7.2, 2 Hz, 1H), 7.97 (d, J = 1.2), 7 Hz, 1H), 7 Hz, 1H	Schm
Y Name M2-amino-phenyl)-4-{{4-	N42-amino-phenyl)-4-{[4- (2-methoxy-ethyl-1-	7[4	1.8 E	Characterization ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s), 8.58 (s), 8.40 (dd, J = 7.2, 2 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.05 90 (m, 2H)
MeOCH ₂ CH ₂ NH amino-6-phenethyl-amino-11,3,5]triazin-2-yl-amino-1-methyl-benzamide		amino-6-phenethyl- amino-[1,3,5]triazin-2-yl- amino]-methyl}- penzamide	2.9.6	6.86 (dd, J = 8.1, 1.2 Hz), 6.76 (dd, J = 7.5, 1.8 Hz), 6.86 (dd, J = 7.5, 1.8 Hz), 6.67 (td, J = 7.5, 1.8 Hz), 6.67 (td, J = 7.8, 1.5 Hz), 6.60-5.50 (m, 3H), 4.75-4.55 (m, 4H), 3.65-3.35 (m, 6H), 3.35-3.20 (s, 3H), 2.95-2.75 (m, 2H).
N42-amino-phenyl)-4-[[4-horo-phenethyl-amino]-6-cyclopropyl-amino]-nethyl-amino]-methyl}-benzamide	5	W(2-amino-phenyl)-4-[[4-4-chloro-phenethyl-amino]-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl]-	1 4 H H S 0.0	¹ H NMR (300 MHz, acetone-d ₆) & (ppm): 9.02 (s, 1H), 8.02-7.91 (m, 2H), 7.58-7.40 (m, 2H), 7.28 (s, 4H), 7.20-7.05 (m, 1H), 6.99 (td, J = 7.5, 1.8 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.67 (t, J = 6.9 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.65-3.40 (bs, 2H), 2.95-2.65 (m, 2H), 0.75-0.55 (m, 2H), 0.55-0.40 (m, 2H).
MK2-amino-phenyl)-4-[[6-cyclopropyl-amino-4(4-methoxy-phenethyl-amino]-11,3,5]triazin-2-yl-amino]-methyll-benzamide	l . <u> </u>	l . <u> </u>	1. 4. £. £. \$	Cyclopropyl-amino-4(4-16-14 NMR (300 MHz, CDCI ₃) & (ppm): 8.55-7.72 (m, methoxy-phenethyl-4H), 7.55-6.75 (m, 9H), 6.75-5.30 (m, 3H), 4.69 (m, amino)-[1,3,5]triazin-2-yl-2H), 3.85 (s, 3H), 3.63 (bs, 2H), 2.86 (m, 3H), 0.85 aminol-methyll-6s, 2H), 0.61 (bs, 2H).
CI (4.2-amino-phenyl)-4-[[4- (3-chloro-phenethyl- amino)-6-cyclopropyl- amino-[1,3,5]triazin-2-yl- amino]-methyl}- benzamide	CI (3-chloro-phenyl)-4-[[4- (3-chloro-phenethyl- amino]-6-cyclopropyl- amino-[1,3,5]triazin-2-yl- amino]-methyl}- benzamide	W(2-amino-phenyl)-4-[[4-3-chloro-phenethyl-amino)-6-cyclopropylamino-[1,3,5]triazin-2-yl-amino]-methyl)-	유 프 · · · · · · · · ·	(3-chloro-phenyl)-4-[14-

EX.	Pd C	×	γ	Name	Characterization	Schm
337	478	,¥ △	OMe	N(2-amino-phenyl) 4-{[6-cyclopropyl-amino-4-(3,4-dimethoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	¹ H NMR (300 M) 1H), 7.96 (d, J = 8 7.29 (d, J = 8.1 H 1H), 6.95-6.72 (m 1H), 6.20-5.60 (m 6H), 3.65-3.42 (m (m, 4H).	18
338	479	\ \	HN - OMe	N-(2-amino-phenyl)-4-{[6-cyclopropyl-amino-4-(3-methoxy-phenethyl-amino)-{1,3,5}triazin-2-yl-amino]-methyl}-benzamide	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.60-7.35 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.99 (td, J = 7.5, 1.5 Hz, 1H), 6.90-6.70 (m, 4H), 6.67 (t, J = 7.8 Hz, 1H), 6.60-5.60 (m, 3H), 4.77-4.50 (m, 4H), 3.76 (s, 3H), 3.65-3.45 (m, 2H), 2.92-2.65 (m, 3H), 0.72-0.42 (m, 4H).	18
339	480	\ \	H.N.	M{2-amino-phenyl}4-{[6-cyclopropyl-amino-4-(2-pyridin-2-yl-ethyl-1-amino]-f1,3,5]triazin-2-yl-amino]-methyl}-benzamide	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.03 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, cyclopropyl-amino-4(2-2H), 7.66 (t, J = 7.5 Hz, 1H), 7.60-7.40 (m, 2H), 7.35-7.08 (m, 3H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), aminol-11,3,5]triazin-2-yl-6.86 (dd, J = 8.1, 1.5 Hz, 1H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.80-3.60 (m, 2H), 3.15-2.90 (m, 2H), 2.90-2.65 (m, 1H), 0.73-0.40 (m, 4H).	. 18
340	481	\ \	₹-	M{2-amino-phenyl}-4-[[6-cyclopropyl-amino-4-(3-pyridin-2-yl-ethyl-1-amino]-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide	N{2-amino-phenyl}-4-{[6-14 NMR (300 MHz, acetone-ds] & (ppm): 9.20-9.00 cyclopropyl-amino-4(3-(m, 1H), 8.70-8.50 (m, 2H), 8.00 and 7.88 (2d, J = pyridin-2-yl-ethyl-1. 7.9 Hz, 2H), 7.75-7.43 (m, 3H), 7.38-6.67 (m, 5H), aminol-methyl}-6.22-5.78 (m, 3H), 4.80-4.55 (m, 4H). 3.61 (bs, 2H), benzamide	18

Cpd X	×		 	Name	Characterization	Schm
482 Cyclopropyl-amino-6-cyclopropyl-amino-6-phenyll-4-cyclopropyl-amino-6-phenyll-0xy-[1,3,5]triazin-2-yl-amino-phenyll-benzamide			N42-amino-p cyclopropyl- phenethyl-ox [1,3,5]triazir methyl]-benz	[(4- nio)-	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.04 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.35-7.15 (m, 6H), 7.00 (td, J = 7.5, 1.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 7.18-6.35 (m, 2H), 4.75-4.30 (m, 6H), 3.10-2.92 (m, 2H), 0.75-0.63 (m, 2H), 0.57-0.48 (m, 2H).	1, 25
A83 Me phenethylam Me phenethylam [1,3,5]triazir methyl-benz			M(2-amino-p methyl-4- phenethylam [1,3,5]triazir methyl]-benz	henyl)-4-[(6- iino- t-2-yl-amino)- amide	"H NMR (300 MHz, acetone-de + D DMSO-de) 8 M2-amino-phenyl)-4-[(6- (ppm): mixture of rotamers, 9.62 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.80-7.44 (m, 3H), 7.40-7.10 (m, 8H), 7.01 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), (1,3,5]triazin-2-yl-amino)-6.67 (t, J = 7.4 Hz, 1H), 4.85 (bs, 2H), 4.72-4.54 (m, 2H), 2.96-2.74 (m, 2H), 2.21 and 2.13 (2s, 3H).	30
484 (4-7-484			N{2-amino-pł amino-6-phen triazin-2-yl-ar methyl}-benz:	.3,5]- e	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): mixture of rotamers, 9.08 (bs, 1H), 8.48·8.36 (m, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.63-7.42 (m, 5H), 7.33 (d, J = 7.7 Hz, 1H), 7.19 (bs, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.35 and 6.25 (2bs, 2H), 4.87 and 4.75 (2d, J = 5.9 Hz, 2H), 4.65 (bs, 2H).	30
485 (2-indanyl-anino-phenyl)-4-[(6-indanyl-anino)-4-indanyl-anino)-4-indanyl-anino)-4-indanyl-anino-phenyl)-indanyl-anino-phenyl	M(2-amino-ph (2-indanyl-am phenyl-[1,3,5 yl-amino]-met	M-2-amino-ph (2-indanyl-am phenyl-[1,3,5] yl-aminol-met benzamide	M{2-amino-pł (2-indanyl-am phenyl-[1,3,5 yl-aminol-met benzamide	•	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): mixture of rotamers, 9.14-8.96 (m, 1H), 8.54-8.30 (m, 2H), 8.09-7.95 (m, 2H), 7.68-7.40 (m, 5H), 7.38-7.08 (m, 6H), 7.03 (t, J = 7.3 Hz, 1H), 6.94-6.76 (m, 2H), 6.71 (t, J = 7.3 Hz, 1H), 5.13-4.54 (m, 5H), 3.49-3.18 (m, 2H), 3.12-2.90 (m, 2H).	30

Example 29

N-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound 39)

Step 1: N-Acetyl-1-piperonylpiperazine (compound 37)

[0171] To a stirred solution at 0°C of 1-piperonylpiperazine 36 (5.00 g, 22.7 mmol) in anhydrous CH_2Cl_2 (60 mL) was added Et_3N (6.33 mL, 45.4 mmol) followed by acetyl chloride (1.94 mL, 27.2 mmol). The reaction mixture was stirred 30 min. at 0°C and then 2 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($MeOH/CH_2Cl_2$: 4/96) to afford the title compound 37 (5.52 g, 21.11 mmol, 93% yield) as a yellow solid. 1H NMR: (300 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 1H), 6.72 (m, 2H), 5.92 (s, 2H), 3.59 (t, J = 5.1 Hz, 2H), 3.44-3.40 (m, 4H), 2.42 (dt, J = 5.1 Hz, 5.1 Hz, 4H), 2.06 (s, 3H).

Step 2: 2-Chloro-4-morpholin-4-yl-6-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-[1,3,5]triazine (compound 38)

[0172] To a stirred solution of 37 (3.00 g, 11.4 mmol) in anhydrous THF (25 mL) at -78° C was slowly added a solution of LiHMDS (11.4 mL, 11.4 mmol, 1 M in THF). The reaction mixture was stirred 1 h at -78° C and a solution of 2,4-dichloro-6-morpholin-4-yl-[1,3,5]triazine (2.69 g, 11.4 mmol) in anhydrous THF (25 mL) was added. The reaction mixture was slowly warmed up at room temperature and the reaction was quenched after 16 h with a saturated aqueous solution of NH₄Cl. The THF was evaporated and the residue was diluted with AcOEt. The organic layer was successively washed with sat. NH₄Cl and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 1/99 \rightarrow 3/97) to afford the title compound 38 (4.84 g, 10.49 mmol, 92% yield) as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.84 (s, 1H), 6.77-6.69 (m, 2H), 5.95 (s, 2H), 3.75-3.43 (m, 16H), 2.42 (m, 4H).

Step 3: N(2-Amino-phenyl)-4-{(4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl)-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound **39**)

[0173] The title compound 39 was obtained following the same procedure as Example 1, step 5. 1 H NMR (CDCl₃) δ (ppm): 7.96 (bs, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.5 Hz, 1H), 7.10 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 6.87-6.81 (m, 3H), 6.75-6.68 (m, 2H), 5.93 (s, 2H), 5.67 (bs, 1H), 4.64 (s, 2H), 3.90 (bs, 2H), 3.75-3.35 (m, 16H), 2.45-2.30 (m, 4H).

Example 40

N-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound 44)

Step 1: N(5-Bromo-pyridin-2-yl)-N'-phenyl-ethane-1, 2-diamine (compound 42)

[0174] A mixture of 2,5-dibromopyridine 40 (2.08 g, 8.6 mmol) and phenyl-1,2-ethyldiamine (1.98 g, 14.6 mmol, 1.7 equiv.) was stirred under nitrogen at 120°C for 6h. After cooling down to room temperature, the solid mixture was ground in a mortar, dissolved in ethyl acetate (200 mL), washed with saturated NaHCO₃ (2 x 50 mL), dried (MgSO₄), filtered and concentrated. After a quick

purification through a short chromatographic column (silica gel, elution 50% ether in hexanes), a pale yellow solid **42** (1.75 g, 6.01 mmol, 70% yield) was obtained. ¹³C NMR (300 MHz, acetone- d_6) δ (ppm): 158.6, 149.6, 148.8, 139.9, 129.8, 117.1, 113.1, 110.8, 106.6, 43.9, 41.5. LMRS = 294.0 (M+1).

Step 2: N(2-aminophenyl)-6(2-phenylamino-ethylamino)-nicotinamide (compound 44)

[0175] A mixture of 5-bromo-2-*N*-alkanyl-2-aminopyridine **42** (352 mg, 1.2 mmol), 1,2-phenylenediamine (3.95 mmol, 3.3 equiv.), Pd(OAc)₂ (0.31 mmol, 26% mol) and 1,1'-bis (diphenylphosphino) ferrocene (124 mg, 0.22 mmol) was suspended in degassed DMF (3mL), treated with diisopropylethyl amine (0.9 mL, 5.2 mmol) and the system flushed with CO. The reaction mixture was warmed up to 60° C and stirred under CO (balloon) for 18 h at this temperature. After evaporation of the DMF under vacuo, the residue was purified through a chromatographic column (silica gel, elution 3% to 6% methanol in dichloromethane) to give 258 mg (0.74 mmol, 62 % yield) of the aminoanilide **44**. ¹H-NMR (CD₃OD-d4), δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J= 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, J= 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H).

Example 41

N-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound 45)

Step 1: N(5-Bromo-pyridin-2-yl)-4-methoxybenzylamine (compound 43)

[0176] A mixture of 2,6-dibromopyridine 41 (6.03 mmol, 2 equiv.) and para-methoxybenzyl amine (413 mg, 3.01 mmol) was stirred under nitrogen at 120°C for 6h. After identical work-up procedure described before and purification through a pad of silica gel (elution 50% ether in hexanes), a pale yellow solid 43 (773 mg, 2.60 mmol, 87% yield) was obtained. 13 C NMR (300 MHz, CDCl₃) δ (ppm): 159.1, 139.7, 132.1, 130.5, 128.9, 127.2, 116.2, 114.3, 104.8, 55.4, 46.0. LMRS = 295.0 (M+1).

Step 2: N(2-amino-phenyl)-6(4-methoxy-benzylamino)-nicotinamide (compound 45)

[0177] Following the procedure described in Example 40, step 2, but substituting 43 for 42, the title compound 45 was obtained in 61% yield.

Example 42

N-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)

Step 2: 3-[6-(2-Phenylamino-ethylamino)- pyridin-3-yl)-acrylic acid tert-butyl ester (compound 46) [0178] In a 50 mL flask, a mixture of 42 (308 mg, 1.05 mmol), tert-butylacrylate (0.8 mL, 5.5 mmol), diisopropylethylamine (0.8 mL, 4.6 mmol), tri-o-tolylphosphine (POT, 192 mg, 0.63 mmol), Pd₂(dba)₃ (73 mg, 0.08 mmol) in anhydrous DMF (4 mL) was stirred at 120°C (preheated oil bath) for 2h under nitrogen. After DMF removal, the crude residue was submitted to a chromatographic purification (column silica gel, 50% ether in hexanes) to afford 316 mg of 46 (88% yield). 13 C NMR (300 MHz, CDCl₃) δ (ppm): 166.6, 159.3, 149.6, 147.8, 140.7, 134.9, 129.1, 119.8, 117.3, 115.9, 112.6, 107.8, 80.0, 43.5, 40.9, 28.1. LRMS = 340.3 (M+1).

Step 3: 3-[6-(2-Phenylamino-ethylamino)- pyridin-3-yl)-acrylic acid (compound 48)

[0179] Ester **46** (0.93 mmol) was dissolved 40 % TFA in dichloromethane (10 mL) and the solution stirred at room temperature overnight. The solvent was removed under *vacuo* distilling with acetonitrile (3x10 mL) and stored under high vacuum for 6h. The solid residue **48** was employed for the next reaction without further purification. LRMS = $284.1 \, (M+1)$.

Step 4: N(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound **50**) [**0180**] A mixture of acid **48** (0.93 mmol), BOP (495 mg, 1.12 mmol) and 1,2-phenylenediamine (124 mg, 1.15 mmol) were dissolved in dry acetonitrile (4 mL) and treated with triethylamine (0.8 mL, 5.7 mmol). The solution was stirred under nitrogen at room temperature for 16h. After concentration under *vacuo*, the crude was purified through chromatographic column (5% methanol in dichloromethane), then was crystallized from chloroform to give **50** (247 mg, 71% yield). 1 H-NMR (DMSO-d6), δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H).

Example 43

N-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)

Step 2: N(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound**51**) [**0181**] Following the procedure described in Example 42, steps 2, 3, 4, but substituting**43**for**42**, the title compound**51** $was obtained in 50% yield (on 2 steps). <math>^1H-NMR$ (CDCl₃), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).

Example 44

4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

Step 1: (4-bromo-benzyl)-carbamic acid pyridin-3-yl-methyl ester (compound 54)

[0182] 4-bromobenzylamine HCl (3.0g, 13.4 mmol) was dissolved in DMF (60 mL) at rt and then $\rm Et_3N$ (4.13 mL, 29.7 mmol) was added dropwise over 10 min to give cloudy solution. To this, DBU (2.42 mL, 16.2 mmol) and 1,1'-carbonyl diimidazole (2.41g, 14.8 mmol) were added. After being stirred for 1 h at rt, 3-pyridylcarbinol (1.44 mL, 14.8 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue obtained was diluted with ether/EtOAc (9:1) and then washed with $\rm H_2O$. The organic layer was dried over $\rm Na_2SO_4$, filtered and then concentrated to give the crude product which was recrystallized from EtOAc to give 2.55g of product **54** (59% yield, LRMS = 323 (M+1).

Step 2: 4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

[0183] Following the procedure described in Example 42, steps 2, 3, but substituting 54 for 42, and acrylic acid for tert-butyl acrylate the title compound 55 was obtained in an overall yield of 20%. 1 H NMR: (DMSO-d6) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).

Example 45

N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound 59)

Step 1: (4-Bromo-benzyl)-(3,4,5-trimethoxy-benzyl)-amine (compound 57)

[0184] To a stirred suspension of K_2CO_3 (522 mg, 3.77 mmol) in dry DMF was added 3,4,5-trimethoxybenzylamine (1.10 mL, 6.44 mmol, 2.2 equiv.) followed by a solution of p-bromo benzylbromide (0.73 g, 2.91 mmol) in dry DMF (8 mL). The mixture was stirred at room temperature under nitrogen for two days in the dark, diluted with dichloromethane (200 mL), washed with brine, dried (MgSO4), filtered and concentrated. The crude residue was purified by chromatographic column on silica gel (elution 5% methanol in dichloromethane) to give 2.59 mmol (89% yield) of

dibenzylamine **57**. ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 152.5, 138.8, 136.1, 135.4, 130.6, 129.2, 119.8, 104.2, 59.9, 55.3, 52.6, 51.7. LRMS = 368.4 (M+1).

Step 2: N(2-Nitro-phenyl)-3-{4-{(3,4,5-trimethoxy-benzylamino}-methyl}-phenyl}-acrylamide (compound 58)

Preparation of the nitroacrylanilide

[0185] To a mixture of 2-nitroaniline (1.73 g, 12.5 mmol), DMAP (321 mg, 2.6 mmol) and 2,6-ditert-butyl-4-methylphenol (308 mg) in dry dichloromethane (50 mL) at 0°C was added triethylamine (10.6 mL, 76 mmol) followed by acryloylchloride (3.2 mL, 38 mmol, 3.0 equiv.), and the mixture was stirred at room temperature for 16h. The solution was diluted with dichloromethane (250 mL), cooled to 0°C and the excess of reagent quenched with saturated NaHCO₃ (stirring for 1 h). The organic layer was then washed (5% KHSO₄, then brine), dried (MgSO₄), filtered and concentrated under reduced pressure. After purification through chromatographic column on silica gel (elution 50% ether in hexanes), 642 mg (3.34 mmol, 27% yield) of the amide was obtained. ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 163.6, 136.0, 135.6, 134.5, 131.3, 128.6, 125.4, 123.1, 121.8. LRMS = 193.2 (M+1).

Step 3: N(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl)-acrylamide (59)

[0186] A mixture of nitro-compound **58** (127 mg, 0.27 mmol), SnCl₂ (429 mg, 2.26 mmol, 8.4 equiv.) and NH₄OAc (445 mg) was suspended in methanol (9.5 mL) and water (1.5 mL), and the mixture was heated at 70°C for 45 min. The mixture was diluted with ethylacetate (100 mL) and washed with brine and then saturated NaHCO₃, dried (MgSO₄), filtered, and concentrated. Purification by chromatographic column on silica gel (elution 5 to 10% methanol in dichloromethane) gave 52 mg (43% yield) of **59**. ¹H-NMR (CDCl₃), δ (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).

Example 46

N-(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}- phenyl)-acrylamide (compound 61)

Step 1: 3-[4-{[Methyl-(3,4,5-trimethoxy-benzyl-amino-methyl-phenyl-N-(2-nitro-phenyl)-acrylamide (compound 60)

[0187] Amine 58 (180.2 mg, 0.38 mmol) was dissolved in 88% of HCO₂H (6 mL), treated with excess of paraformaldehyde (7.67 mmol) and the mixture stirred at 70°C for 2.5h. A saturated NaHCO₃ solution, was added slowly, extracted with dichloromethane (2 x 75 mL), dried (MgSO₄), filtered and concentrated. After chromatographic column on silica gel (elution 3 to 5% methanol in dichloromethane), pure N-methyl amine 60 (118 mg, 63% yield) was obtained. ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 164.5, 153.1, 143.5, 142.3, 136.8, 136.1, 136.0, 135.3, 134.9, 132.9, 129.3, 128.2, 125.8, 123.1, 122.2, 120.3, 105.4, 62.2, 61.2, 60.8, 56.0, 42.5. LRMS = 492.5 (M+1).

Step 2: N(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}-phenyl)-acrylamide (compound **61**)

[0188] Following the procedure described in Example 45, step 3, but substituting the nitro-compound 60 for 58, the title compound 61 was obtained in 72% yield. 1 H-NMR (DMSO-d6), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H).

Example 47

N-(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)

Step 1: Methyl-3-(4-amino-phenyl)-acrylate hydrochloride (compound 63)

4-amino-cinnamic acid (10.41 g, 0.052 mol) was dissolved in methanol (100 mL) at rt. A solution of HCl in dioxane (15.6 mL, 4 N) was then added. The reaction mixture was heated at reflux overnight. The clear solution was evaporated to a half volume and then settled down at rt. The white suspension obtained was collected by vacuum filtration. The mother liquid was evaporated again to a quart volume and cooled down to rt. The suspension was filtered again. The combined the solid collected from two filtration was dried in vacuo to give 7.16 g of 63 (64.3% yield). LRMS: 178 (M+1).

Step 2: Methyl-3-{4-(4-methoxy-benzylamino)-phenyl}- acrylate hydrochloride (compound 64)

To a suspension of compound 63 (3.57 g, 16.7 mmol) in DMF (30 mL) was added Et₃N. [0190] after 10 min 4-methoxybenzyl chloride (2.0 g, 12.8 mmol), Nal (0.38 g, 2.6 mmol) and K₂CO₃ (3.53 g, 25.5 mmol) were added successively. The mixture was heated at 60°C overnight and evaporated to dryness. The residue was partitioned between NaHCO3 sat. solution (50 mL) and EtOAc (50mLx3). The combined organic layers were washed with brine and then evaporated to dryness. The residue was purified by flash chromatography and then recrystallized from isopropylalcohol to give 1.16 g **64** (yield 30.6%, LRMS = 298) and 1.46g of **63** (49% recovered yield).

Step 3: N(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)

[0191] Following the procedure described in Example 42, step 4, but substituting 64 for 48, the title compound 65 was obtained in 32% yield. ¹H NMR: (DMSO-d6) δ (ppm): 9.15 (s, 1H), 7.24 –7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).

Example 49 72: ArZ = MeOPhCO

Example 48

N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (compound 71)

Step 1: N(4-lodo-phenyl)(3-phenyl-allyl)-amine (compound 69)

[0192] Following the procedure described in Example 47, step 2, but substituting 68 for 63, the title compound 69 was obtained in 70% yield. LRMS = $288 \, (M+1)$

Step 2: N(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (71)

[0193] Following the procedure described in Example 42, steps 2, 4, but substituting 69 for 42, and acrylic acid for tert-butyl acrylate the title compound 71 was obtained in an overall yield of 60%. 1 H NMR: (DMSO-d₆) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).

Example 49

N-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

Step 1: N(4-lodo-phenyl)-4-methoxy-benzamide (compound 70)

[0194] Following the procedure described in Example 47, step 2, but substituting 68 for 63, the title compound 70 was obtained in 90% yield. LRMS = $354.0 \, (M+1)$

Step 2: N(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

[0195] Following the procedure described in Example 42, steps 2, 4, but substituting 70 for 42, and acrylic acid for tert-butyl acrylate the title compound 72 was obtained in an overall yield of 90%. 1 H NMR: (DMSO-d₆) δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).

Example 50

N-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 76)

Step 1: N(5-Bromo-pyridin-2-yl)-ethane-1,2-diamine (compound 73)

[0196] Following the procedure described in Example 40, step 1, but using 1,2-diaminoethane as alkyl amine, the title compound **73** was obtained in 84% yield. 13 C NMR (300 MHz, CD₃OD): 159.1, 148.7, 140.7, 111.7, 107.2, 44.3, 41.7. LRMS = 218.1 (M+1)

Step 2: 3-[2-(5-Bromo-pyridin-2-ylamino)-ethyl]-3H-quinazolin-4-one (compound 75)

[0197] A suspension of primary amine **73** (1.17 g, 5.40 mmol) and isatoic anhydride **74** (880 mg, 5.40 mmol) in methanol (25 mL) was stirred for 3 h at 50°C and then concentrated. The resulting oily residue was dissolved in 88% formic acid (20 mL) and refluxed overnight. After removal of formic acid, the solid residue was purified through column chromatography on silica gel (5% methanol in dichloromethane) to give 1.24 g (3.6 mmol, 67% yield) of **75**. 13 C NMR (300 MHz, CDCl₃): 161.6, 156.8, 147.7, 147.6, 147.2, 139.8, 134.5, 127.4, 126.8, 126.3, 121.6, 110.1, 107.0, 46.3, 40.1. LRMS = 347.1 (M+1).

Step 3: N42-aminophenyl)-3-16-[2-14-oxo-4H-quinazolin-3-yl)-ethylamino-pyridin-3-yl)-acrylamide (compound 76)

[0198] Following the procedure described in Example 42, steps 2 to 4, but substituting 75 for 42, the title compound 76 was obtained in an overall yield of 68 %. 1 H-NMR (DMSO-d6), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).

Example 51

N-(2-aminophenyl)-3-(6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 78)

Step 2: 4-Benzyl-1-[2-(5-bromo-pyridin-2-ylamino)-ethyll-piperazine-2,6-dione (compound 77)

[0199] A suspension of benzyliminodiacetic acid (702 mg, 3.15 mmol) and acetic anhydride (15 mL) was stirred at 120°C for 45 min. The reaction mixture was diluted with dry toluene and concentrated in *vacuo* to remove the volatiles. The residue was dissolved in dry toluene (15 mL) and transferred via cannula to a reaction flask containing the amine **73** (475 mg, 3.2 mmol). The mixture was heated at 90°C for 16 h, concentrated and chromatographed by column on silica gel (elution 5% methanol in dichloromethane) to give 684mg (1.70 mmol, 54% yield) of **77**.

Step 3: N(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylaminol-pyridin-3-yl}-acrylamide (compound 78)

[0200] Following the procedure described in Example 42, steps 2 to 4, but substituting 77 for 42, the title compound 78 was obtained in an overall yield of 60%. ¹H-NMR (CD₃OD-d4), δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H).

Example 52

(E)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-cinnamide (compound 83)

Step 1: 4,6-Dichloro-2-(2-indanyl-amino)-[1,3,5]triazine (compound 79)

[0201] To a stirred solution at -78° C of cyanuric chloride (13.15 g, 71.33 mmol) in anhydrous THF (100 mL) under nitrogen was slowly canulated a solution of 2-aminoindan (10.00 g, 75.08 mmol), iPr₂NEt (14.39 mL, 82.59 mmol) in anhydrous THF (60 mL). After 50 min, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat*. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 2/98 \rightarrow 5/95) and by co-precipitation (AcOEt/hexanes) to afford the title compound **79** (18.51 g, 65.78 mmol, 92% yield) as a beige powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.29-7.18 (m, 4H), 6.02 (bd, J = 6.3 Hz, 1H), 4.94-4.84 (in, 1H), 3.41 (dd, J = 16.2, 6.9 Hz, 2H), 2.89 (dd, J = 16.1, 4.5 Hz, 2H).

Step 2: 2-(4-Bromo-benzyl-amino)-4-chloro-6-(2-indanyl-amino)-[1,3,5]triazine (compound 80)

[0202] To a stirred solution at room temperature of **79** (2.68 g, 9.52 mmol) in anhydrous THF (50 mL) under nitrogen were added i-Pr₂NEt (4.79 mL, 27.53 mmol) and 4-bromobenzylamine.HCl (2.45 g, 11.01 mmol), respectively. After 17 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and

concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: $3/97 \rightarrow 5/95$) to afford the title compound **80** (4.00 g, 9.29 mmol, 97% yield) as a white powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 7.52-7.42 (m, 2H), 7.26-7.11 (m, 6H), 6.51 and 6.12 (2 m, 1H), 5.72-5.46 (m, 1H), 4.94-4.64 (m, 1H), 4.62-4.46 (m, 2H), 3.43-3.16 (m, 2H), 2.92-2.74 (m, 2H).

Step 3: 4-Amino-2-(4-bromo-benzyl-amino)-6-(2-indanyl-amino)-[1,3,5]triazine (compound 81)

[0203] In a 75 mL sealed flask, a solution of 80 (2.05 g, 4.76 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH₃ gas for 5 min, and warmed to 140°C for 18 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH₃ gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into 1N HCl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 5/95) to afford the title compound 81 (1.96 g, 4.76 mmol, quantitative yield) as a colorless foam. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.43 (d, J = 8.2 Hz, 2H), 7.25-7.12 (m, 6H), 5.70-5.10 (m, 2H), 5.00-4.65 (m, 3H), 4.52 (bs, 2H), 3.40-3.10 (m, 2H), 2.90-2.65 (m, 2H).

Step 4: (E)-4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl]-N-[2-(N-t-butoxycarbonyl)-amino-phenyl]-cinamide (compound 82)

Preparation of N-[2-(N-t-Butoxycarbonyl)-amino-phenyl]-acrylamide

[0204] Following the procedure described in Example 45, step 2, but substituting the nitro-compound 2-(*N*-t-butoxycarbonyl)-amino-aniline for 2-nitroaniline, the title compound was obtained in 77% yield. 1 H NMR (300 MHz, CDCl₃) δ (ppm): 8.51 (bs, 1H), 7.60-7.45 (m, 1H), 7.38-7.28 (m, 1H), 7.20-7.05 (m, 2H), 6.98 (bs, 1H), 6.41 (dd, J = 17.0 Hz, 1.1 Hz, 1H), 6.25 (dd, J = 16.9 Hz, 10.0 Hz, 1H), 5.76 (dd, J = 10.2 Hz, 1.4 Hz, 1H), 1.52 (s, 9H).

[0205] In a 50 mL sealed flask, a solution of 81 (300 mg, 0.73 mmol), the acrylamide (230 mg, 0.88 mmol), Et_3N (407 μ l, 2.92 mmol), tri-o-tolylphosphine (POT, 13 mg, 0.04 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol) in anhydrous DMF (10 mL) was stirred at room temperature, saturated with N_2 gas for 15 min, and warmed to 100°C for 15 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4CI , and diluted with AcOEt. After

separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 2/98→5/95) to afford the title compound 82 (240 mg, 0.41 mmol, 56% yield) as a beige solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.46 (bs, 1H), 7.71 (bd, J = 15.7 Hz, 1H), 7.62-7.05 (m, 13H), 6.54 (bd, J = 15.9 Hz, 1H), 5.95-4.90 (m, 4H), 4.85-4.48 (m, 3H), 3.40-3.14 (m, 2H), 2.90-2.70 (m, 2H), 1.52 (s, 9H).

Step 5: (E)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl]-N-(2-amino-phenyl)cinnamide (compound 83)

To a stirred solution at room temperature of 82 (230 mg, 0.39 mmol) in CH₂Cl₂ (5 mL) [0206] was added TFA (1 mL, 95% in water). After 18 h, the reaction mixture was poured into a saturated aqueous solution of NaHCO3, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NaHCO₃, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 5/95) to afford the title compound 83 (170 mg, 0.35 mmol, 89% yield) as a yellow solid. ${}^{1}H$ NMR (300 MHz, acetone-d₆) δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-102.80 (m, 2H).

- a. TI2O / Py / DMAP / 0 C
- b. p-methoxybenzylamine / 120 C
- c. 1,2-phenylenediamine / CO (40 psi) / Pd(OAc)2 / dppf / DMF / DIPEA / 70 C
- d. t Butytacrylate / Pd₂(dba)₃ / POT / DMF / DIPEA / 120 C e. TFA / DCM / rT

f. 1,2-phenylenediamine / BOP/ DMF / TEA / rT

Example 53

N-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)

Step 1: 2,6-ditrifluoromethanesulfonyloxy-quinoline (compound 85):

[0207] A solution of 2,6-dihydroxyquinoline **84** (1.254 g, 7.78 mmol) and DMAP (a few crystals) in dry pyridine (15 mL) was treated with neat trifluoromethanesulfonic anhydride (5.2 g, 18,4 mmol, 1.2 equiv.) and stirred at 0°C for 5 h. This solution was then poured on a mixture brine/sat NaHCO₃ and extracted with dichloromethane (2 x 150 mL), dried (MgSO₄), filtered and concentrated. Purification by column chromatography on silica gel (30% to 50% ether in hexanes) gave 2.58 g (6.1 mmol, 78% yield) of **85**. 13 C NMR (300 MHz, CDCl₃): 154.5, 147.8, 144.6, 142.0, 131.6, 127.8, 124.9, 119.3, 118.7, 114.9. LRMS = 426.0 (M+1).

Step 2: N(2-aminophenyl)-2-(4-methoxy-benzylamino)-guinolin-6-yl-amide (compound 87)

[0208] Following the procedure described in Example 40, steps 1, 2, but substituting **85** for **40**, the title compound **87** was obtained in 92% yield. 1 H-NMR (DMS0- 1 d6), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).

Example 54

N-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88) Step 3: N-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

[0209] Following the procedure described in Example 42, steps 1 to 4, but substituting **85** for **40**, the title compound **88** was obtained in an overall yield of 71%. 1 H-NMR (DMSO-d6), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).

Examples 55-84

[0210] Examples 55 to 84 describe the preparation of compounds **89** to **118** using the same procedures as described for compounds **44** to **88** in Examples 40 to 54. Characterization data are presented in Tables 3a-d.

Table 3a

Characterization of Compounds Prepared in Examples 42-84

Schm	m	4	Ŋ	т
Characterization	¹ H-NMR (DMSO-d6) , δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H)	¹ H NMR: (DMSO-d6) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).	¹ H-NMR (CDCI₃), 8 (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).	¹ H-NMR (DMSO-d6), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.83
Name	N{2-aminophenyl)-3- [6-{2-phenylamino- ethylamino)-pyridin- 3-yl]-acrylamide	[4-[2-(2-amino- phenylcarbamoyl)- vinyl]-phenyl}- carbamic acid pyridin-3-yl methyl ester	N42-aminophenyl}-3- {4-[(3,4,5- trimethoxy- benzylamino}- methyl]-phenyl}- acrylamide	NK2-aminophenyl)-3- [6-(4-methoxy- benzylamino)- pyridin-3-yl]-2-
~	Σ	Ι	I	Me
7		끙	끙	공
>	Z	ъ ъ	HO CH	Z
M	IZ	0=\ 0=\ ZI	MeO N. H. H. MeO OMe	MeO
Cpd.	50	55b	59	61b
Ex.	42	44	45	46

Schm	1H), 7.24 (m, 2H), 6 (d, J = 6	_	1H), 7.45 2H), 7.34 6.8 Hz, 78 (d, J = 7 63-6.55 N, 3.95		
Characterization	¹ H NMR: (DMSO-d6) & (ppm): 9.15 (s, 1H), 7.24 –7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).	tH), 4.84 (s, 2H), 4.22 (d	¹ H NMR: (DMSO-d₆) 5 (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).	¹ H NMR: (DMSO-d₆) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H). ¹ H NMR: (DMSO-d₆) δ (ppm): 9.4 (bs, 1H), 7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).	¹ H NMR: (DMSO-d ₆) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 5.4 Hz, 2H), 7.36 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.95 (bs, 2H), 6.95.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H). ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.4 (bs, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (m, 2H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H). ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).
3	¹ H NMR: (DMSO- -7.38 (m, 6H), 6.8 6.49-6.60 (m, 4H), 5.77 Hz, 2H).	6.49-6.60 (m, 4H), 5.77 Hz, 2H). 1H NIMR: (DMSO-	(d, J = 6.9 Hz, 2H) (d, J = 7.4 Hz, 2H) 2H), 6.93 (dt, J = 7.9 Hz, 1H), 6.69 (m, 4H), 6.44-6.37 (bs, 2H).	(d, J = 6.9 Hz, 2H) (d, J = 7.4 Hz, 2H) 2H), 6.93 (dt, J = 7.9 Hz, 1H), 6.69 (m, 4H), 6.44-6.37 (bs, 2H). 1H NMR: (DMSO-7.60(d, J = 8.5 Hz (d, J = 7.7 Hz, 1H) 6.77 (m, 3H), 6.62 (m, 2H), 4.98 (bs,	(d, J = 6.9 Hz, 2H) (d, J = 7.4 Hz, 2H) 2H), 6.93 (dt, J = 7.9 Hz, 1H), 6.69 (m, 4H), 6.44-6.37 (bs, 2H) 14 NMR: (DMSO-7.60(d, J = 8.5 Hz (d, J = 7.7 Hz, 1H) 6.77 (m, 3H), 6.62 (m, 2H), 4.98 (bs, 1H) 6.77 (m, 2H), 4.98 (bs, 1H) 6.77 (m, 1H) 6.7 (m, 2H), 4.98 (bs, 1H) 6.7 (m, 2H), 6.62 (dd, J = 8.0 Hz, 1H) 6.7 (dd, J = 1.9 Hz, 1H) 6.7 (dd, J = 8.0 Hz, 1H)
Name	M{2-amino-phenyl)- 3-[4-(4-methoxy- benzylamino)- phenyl]-acrylamide	enzylamino)- henyl]-acrylamide	M-2-Amino-phenyl)- 3-(4-styrylamino- phenyl)-acrylamide	M-2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide phenyl)-acrylamide N-{4-{2-{2-Amino-phenyl}-vinyl}-phenyl}-4- methoxy-benzamide	N42-Amino-phenyl)-344-styrylamino- phenyl)-acrylamide phenylcarbamoyl)- vinyl]-phenyl}-4- methoxy-benzamide N42-aminophenyl}-3- {6-[244-oxo-4+ quinazolin-3-yl}- ethylamino]-pyridin- 3-yl}-acrylamide
	N G G		Г		
	끙	i i		끙	
	ъ В	품		끙	- 등 2
A	MeO	Meo		MeO NI	
Cpd.	65	7.1		72	72 72 76
EX.	47	48	:	49	50

Cpd.		M	>	7	~	Name	Characterization	Schm
83 N N N N N N N N N N N N N N N N N N N	HN NHN		Ж	СН	I	(E) 4-{[4-Amino-6-(2-indanyl-amino}-{1,3,5]triazin-2-ylamino}-methyl}-N-(2-amino-phenyl)-cinamide	¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).	6
89 MeO MeO			Z	СН	н	M(2-aminophenyl)-3- [6-(4-methoxy- benzylamino)- pyridin-3-yl]- acrylamide	¹ H-NMR (DMSO- <i>d6</i>), δ (ppm): 9.24 (bs, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 5.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.90 (m, 1H), 6.88 (dd, J = 8.5 Hz, 2H), 6.74 (d, J = 6.9 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.45 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H).	ю
NH N			Z	НЭ	Н	N-(2-aminophenyl)-3- {6-{(pyridin-3- ylmethyl)-amino]- pyridin-3-yl}- acrylamide	¹ H-NMR (CD₃0D-44) , δ (ppm): 8.47 (bs, 1H), 8.33 (bs, 1H), 8.02 (m, 1H), 7.73 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.66 (t, J = 7.9 Hz, 1H), 6.53 (m, 2H), 4.54 (m, 2H), 3.59 (bs, 2H).	က
91 N N	,		Z	H5	I	N42-aminophenyl)-3- {6-[(pyridin-4- ylmethyl)-amino]- pyridin-3-yl)- acrylamide	¹ H-NMR (DMSO-46) , 5 (ppm): 9.27 (bs, 1H), 8.48 (dd, J = 1.6 Hz, 4.4, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.70 (m 2H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (m 3H), 6.90 (t, J = 6.9 Hz, 1H), 6.73 (d, J = 6.9 Hz, 1H), 6.58 (m 4H), 4.98 (bs, 2H), 4.57 (d, J = 6.0 Hz, 2H).	ю

F				
Schm	m	т	m	m
Characterization	¹ H-NMR (DMSO-46) , 6 (ppm): 9.24 (bs, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 7.60 (t, J = 5.8 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.36 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.73 (dd, J = 6.9 Hz, 1.0 Hz, 1H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.50 (d, J = 6.0 Hz, 2H).	¹ H-NMR (DMSO-46), 8 (ppm): 9.24 (bs, 1H), 8.17 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.60 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.89 (dt, J = 8.0 Hz, 1.6 Hz, 1.H), 6.73 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.58 (m 3H), 4.92 (bs, 2H), 4.53 (d, J = 6.0 Hz, 2H)	¹ H-NMR (DMSO-46), 5 (ppm): 9.22 (bs, 1H), 8.18 (ds, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.22 (m 7H), 6.90 (t, J = 7.7 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.29 (dt, J = 7.7 Hz, 6.0 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.84 (m, J = 7.7 Hz, 2H).	¹ H-NWR (DMSO-46), 8 (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (m, 1H), 6.91 (m, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.71 (s, 3H), 3.47 (dd, J = 7.3
Name	N42-aminophenyl}-3- [6-{4-fluoro- benzylamino}- pyridin-3-yl]- acrylamide	N-(2-aminophenyl)-3- (6-benzylamino- pyridin-3-yl)- acrylamide	N(2-aminophenyl)-3- [6-(3-phenyl- propylamino)- pyridin-3-yl]- acrylamide	N-(2-aminophenyl)-3- {6-[2-(4-methoxy- phenyl)-ethylamino]- pyridin-3-yl}- acrylamide
~	I	π	I	Ξ
7	Ю	СН	ᆼ	Н
7	Z	Z	Z	Z
M	NI N	H H	ZI	MeO
Cpd.	92	93	94	95
Ex.	58	29	09	61

7.31 (d, J = 7.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 6.78 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 4.30 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.67 (m, 2H), 7.17 (m, 2H), 6.98 (dt, J = 13.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.68 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08						
6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 1.4-NMR (CD₃0D-d4) , 8 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.98 (dt, J = 13.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08	5.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 'H-NMR (CD₃OD-d4) , 5 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.96 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H).	6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 14-NMR (CD₃OD-d4) , 8 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.9 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). 1.1. NNMR (acetone-d6) , 8 (ppm): 8.75 (bs, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.69 (d,	6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 14-NMR (CD₃OD-d4), 5 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz) 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). 14-NMR (acetone-d6), 8 (ppm): 8.75 (bs, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 7.94 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 6.83	6.68 (d, $J = 8.5 \text{ Hz}$, $2H$), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, $J = 5.5 \text{ Hz}$, 2H), (bs, 2H). 4.4.39 (d, $J = 5.5 \text{ Hz}$, 2H), (bs, 2H). 4.8.05 (d, $J = 1.9 \text{ Hz}$, 1H), 7.67 (m, 2H), 7.49 (d, $J = 15.7 \text{ Hz}$, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.98 (dt, $J = 13.7 \text{ Hz}$, 7.7 Hz, 1H), 6.83 (dd, $J = 8.0 \text{ Hz}$, 1.1 Hz, 1H), 6.69 (dt, $J = 9.1 \text{ Hz}$, 1.4 Hz, 1H), 6.58 (d, $J = 8.8 \text{ Hz}$, 1H), 4.15 (t, $J = 7.1 \text{ Hz}$, 2H), 6.51 (d, $J = 8.8 \text{ Hz}$, 1H), 4.15 (t, $J = 7.1 \text{ Hz}$, 2H), 3.29 (m, 2H), 2.08 (m, $J = 6.9 \text{ Hz}$, 2H). 4.55 (d, $J = 1.9 \text{ Hz}$, 1H), 7.69 (d, $J = 8.2 \text{ Hz}$, 1H), 7.55 (d, $J = 8.2 \text{ Hz}$, 1H), 7.55 (d, $J = 1.9 \text{ Hz}$, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, $J = 6.6 \text{ Hz}$, 1H), 6.93 (m, 2H), 7.34 (bs, $J = 6.3 \text{ Hz}$, 2H), 4.65 (bs, 2H).	6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). 1.4-NMR (CD₃OD-44) , 6 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, = 15.7 Hz, 1H), 7.67 (m, 2H), 7.49 (d, 1 = 15.7 Hz, 1H), 6.83 (dd, J = 8.0 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 (m, J = 6.9 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). 14NMR (acetone-46) , 8 (ppm): 8.75 (bs, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.43 (m, 2H), 7.34 (t, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (m, 3H), 4.71 J = 6.3 Hz, 2H), 4.65 (bs, 2H). 14NMR (acetone-46) , 8 (ppm): 8.81 (bs, 1H), 1.4.1 Hz, 1.4.2 Hz, 1.4.3 (m, 2H), 1.4.4 Hz, 1H), 6.67 (m, 3H), 4.71 J = 6.3 Hz, 2H), 1.4.5 (bs, 2H).	6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). **H-NMR (CD₃OD-d4), 5 (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). **H-NMR (acetone-d6), 5 (ppm): 8.75 (bs, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.8 Hz, 1H), 6.67 (m, 3H), 4.71 (d, J = 8.0 Hz, 2H), 1H), 6.67 (m, 3H), 4.71 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 15.7 Hz, 2H), 7.66 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.40 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.40 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.40 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.40 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.40 (d, J = 15.7 Hz, 2H), 7.40 (d, ZH),
30D-44), 8 (ppm): .9 Hz, 1H), 7.67 (n. 4), 7.28 (m, 2H), 7. Hz, 7.7 Hz, 1H), 6.51 5.69 (dt, J = 9.1 H; 6.51 5.7 Hz, 1H), 6.51	30D-44), 8 (ppm): .9 Hz, 1H), 7.67 (r. 1), 7.28 (m, 2H), 7. Hz, 7.7 Hz, 1H), 6.5.69 (dt, J = 9.1 H; 5.7 Hz, 1H), 6.51 J = 7.1 Hz, 2H), 3.7 z, 2H).	30D-44), δ (ppm): 9 Hz, 1H), 7.67 (n, 4), 7.28 (m, 2H), 7. Hz, 7.7 Hz, 1H), 6.51, 5.69 (dt, J = 9.1 Hz, 5.7 Hz, 1H), 6.51, 1 Hz, 2H), 3.7 Lz, 2H). 2, 2H). stone-46), δ (ppm): 9 Hz, 1H), 7.69 (c, 7.6	3 0D-44) , δ (ppm): 9 Hz, 1H), 7.67 (n 1), 7.28 (m, 2H), 7. (n Hz, 7.7 Hz, 1H), 6.51 5.7 Hz, 1H), 6.51 1 = 7.1 Hz, 2H), 3.7 2, 2H). 2, 2H). 2, 2H). 2, 2H). 3tone-d6), δ (ppm) 2, 2H). 3tone-d6), δ (ppm)	¹ H-NMR (CD₃0D-d4) , δ (ppm): 8.05 (d, J = 1.9 Hz, 1H), 7.67 (n = 15.7 Hz, 1H), 7.28 (m, 2H), 7. (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.51 (dt, J = 15.7 Hz, 1H), 6.51 (m, J = 6.9 Hz, 2H). 1.11, 4.15 (t, J = 7.1 Hz, 2H), 3.2 (m, J = 6.9 Hz, 2H). 1.14, 4.15 (t, J = 7.1 Hz, 2H), 3.2 (m, J = 6.9 Hz, 2H). 1.15, 4.15 (d, J = 1.9 Hz, 1H), 7.69 (cools, 2.16) (cools, 2.16) (cools, 3.28) (cools, 3.28) (dools, 3.2	30D-44), 8 (ppm): 9 Hz, 1H), 7.67 (n, 4), 7.28 (m, 2H), 7.67 (n, 2H), 7.7 Hz, 1H), 6.51, 6.5 7 Hz, 1H), 6.51 1 = 7.1 Hz, 2H), 3.2 2H). 2, 2H). 2, 2H). 2, 2H). 2, 2H). 3, 2H). 3, 2H). 4, 2H, 1H), 7.69 (c, 2H). 5, 4 Hz, 1H), 7.43 1 = 6.6 Hz, 1H), 6.4 14, 1.4 Hz, 1H), 6.4 17, 1.4 Hz, 1H), 6.6 18, 1.4 Hz, 1H), 6.6 19, 11, 10, 6.6 10, 11, 10, 6.6 11, 11, 10, 6.6 12, 11, 11, 10, 6.6 13, 11, 11, 10, 6.6 14, 11, 11, 10, 6.6 15, 11, 11, 10, 6.6 16, 11, 11, 11, 11, 11, 11, 11, 11, 11,	30D-44), 8 (ppm): 9 Hz, 1H), 7.67 (n, 4), 7.28 (m, 2H), 7.67 (n, 2H), 7.7 Hz, 1H), 6.51, 6.5 7 Hz, 1H), 6.51 2, 2H). 2, 2H). 2, 2H). 2, 2H). 2, 2H). 3, 2H). 3, 2H). 4, 6, 6, Hz, 1H), 7.43 3, 6, 6, Hz, 1H), 6, 6, 1H, 6, 6, 1H, 7.43 1, 6, 1H, 7.43 1, 1, 4, Hz, 1H), 6, 6, 1H, 6, 6, 1H, 6, 1H, 6, 1H, 6, 1H, 6, 1H, 7.69 (n, 1), 7.69 (n, 1), 7.69 (n, 1), 7.65 (n, 1), 7.65 (n, 1), 7.65 (n, 1), 7.69 (n, 1), 7.60 (n, 1), 7.69
at, J = 15.7 Hz, 1H), 7. at, J = 13.7 Hz, 7 1.1 Hz, 1H), 6.69 5.58 (d, J = 15.7 Hz), 4.15 (f. 1 = 7	(dt, J = 13.7 Hz, 1H), 7.2(dt, J = 13.7 Hz, 7.7 11.1 Hz, 1H), 6.69 (d 6.58 (d, J = 15.7 Hz 1H), 4.15 (t, J = 7.1 (m, J = 6.9 Hz, 2H).	at, J = 15.7 Hz, 1H), 7. at, J = 13.7 Hz, 7 1.1 Hz, 1H), 6.69 5.58 (d, J = 15.7 Hz), 4.15 (t, J = 7 1.1 H, 4.1	15. (17, 111), 7. (14, 111), 7. (14, 111), 6.69 (17, 111), 6.69 (17, 111), 4.15 (1, 1 = 7, 111), 4.15 (1, 1 = 7, 111), 4.15 (1, 1 = 7, 111), 4.15 (1, 1 = 7, 111), 4.15 (1, 1 = 1, 111), 5.23 (1, 1 = 1, 11, 111), 7.19 (1, 1 = 6, 111), 7.19 (1,	at, J = 15.7 Hz, 1H), 7. at, J = 13.7 Hz, 7 Hz, 7 at, J = 13.7 Hz, 1H), 6.69 bi.58 (d, J = 15.7 Hz), 4.15 (t, J = 7 at, J = 6.9 Hz, 2H action (H), 4.15 (d, J = 1.9 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) bi.55 (d, J = 15.4 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz) constant (H), 7.19 (d, J = 6, 1.5 Hz)	= 15.7 Hz, 1H), 7. dt, J = 13.7 Hz, 7 dt, J = 13.7 Hz, 7 1.1 Hz, 1H), 6.69 5.58 (d, J = 15.7 Hz, 2H H. NMR (acetone 3.23 (d, J = 1.9 Hz, 2H), 7.19 (d, J = 6 dd, J = 8.0 Hz, 1. H-NMR (acetone 15.4 Hz, 1. H-NMR (acetone 16.3 Hz, 1. H-NMR (acetone 16.3 Hz, 1. H-NMR (acetone 16.4 J = 1.9 Hz, 1. H-NMR (acetone	15.7 Hz, 1H), 7.1 16.7 Hz, 1H), 6.69 (d, J = 15.7 Hz, 2H 17.8 Hz, 1H), 6.69 (d, J = 15.7 Hz, 2H 17.9 Hz, 2H 18.0 Hz, 2H 19.0 Hz, 2H 19.0 Hz, 2H 19.0 Hz, 2H 19.0 Hz, 1.1 19.0 H
M(2-aminophenyl)-3- = [6-(3-imidazol-1-yl- (c propylamino)- 1 pyridin-3-yl]- acrylamide 1	enyl}-3- -1-yl-	-1-yl- -1-yl- enyl}-3-	enyl}-3- -1-yl- enyl}-3-	£ . £	5. 5.	<u> </u>
I	I	I	т т	т т	т <u>т</u>	т т т
万	ᆼ	ਲ ਲ	ਲ ਲ	5 5	5 5	5 5 5
 Z						
			\	~~~ ~~~~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	NH NH	AT ST
			86	86	86	86 66
			64	64	64	64

Schm	т	т	m	4	
Characterization	¹ H-NMR (DMSO-d6), δ (ppm): 9.25 (bs, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.67 (m, 2H), 7.42 (d, J = 15.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.08 (dt, J = 9.3 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 1.9 Hz, 2H), 6.90 (dt, J = 7.3 Hz, 1.4 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.92 (bs, 2H), 4.56 (d, J = 6.0 Hz, 2H).	¹ H-NMR (DMSO-46), 8 (ppm): 9.25 (bs, 1H), 8.14 (bs, 1H), 7.86 (m, 6H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.90 (dt, J = 8.8 Hz, 1.1 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.96 (bs, 2H), 4.63 (d, J = 5.8 Hz, 2H).	¹ H-NMR (DMSO-d6), 6 (ppm): 9.28 (bs, 1H), 8.17 (bs, 1H), 7.66 (d, J = 5.8 Hz, 2H), 7.37 (m, 6H), 6.88 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1H), 6.59 (m 3H), 4.55 (d, J = 5.8 Hz, 2H), 3.96 (s, 2H), 3.37 (bs, 4H).	¹ H NMR: (DMSO-d6) & (ppm): 9.36 (s, 1H), 8.57 (s, 1H), 8.51 (d, J = 4.6 Hz, 1H), 7.91 (m, 1H), 7.77 (d, J = 7.68 Hz, 1H), 7.28-7.57 (m, 7H), 6.88 (dd, J = 15.66 Hz, 4.4 0 Hz, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.01 (s, 2H), 4.93 (bs, 2H), 4.10 (d, J = 6.04 Hz, 2H).	
Name	M{2-aminophenyl}-3- [6-(3,5-difluoro- benzylamino}- pyridin-3-yl}- acrylamide	N-(2-aminophenyl)-3- [6-(3-trifluoromethyl- benzylamino)- pyridin-3-yl]- acrylamide	3-[6-(3-aminomethyl-benzylamino)- pyridin-3-yll-N-(2-aminophenyl)-acrylamide	[4-[2-42-amino-phenylcarbamoyl)-vinyl]-benzyl]-carbamic acid pyridin-3-yl methyl ester	. 0/01/7/07
~	I	I	工	Ξ	
7	용	끙	픙	Н	
>	z	z	Z	СН	
A	ZI SI	ZI Š Š	NH Z	O O N	
Cpd.	100	101	102	104	
E.	99	29	89	70	_

	×	⊁	2	R	Name	Characterization	Schm
					N42-aminopheny()-3-	¹ H-NMR (acetone-d6), δ (ppm): 8.49 (bs, 1H),	
IZ ((4-[(3,4,5-	8.41 (d, J = 7 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H),	
<u>}</u>	_	7	5		trimethoxy-	7.56 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H),	L
Meo)	=	5	=	phenylamino)-	7.07 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.76 (m,	Ω
OMe					methyll-phenyl}-	1H), 6.74 (m, 1H), 5.99 (s, 2H), 4.36 (s, 2H), 3.69	
		\neg			acrylamide	(s, 6H), 3.68 (bs, 2H), 3.67 (s, 3H).	
						¹ H-NMR (CDCl ₃), δ (ppm): 7.70 (bs, 1H), 7.43 (d,	
			•		M2-aminophenyl)-3-	J = 7.4 Hz, 1H), 7.33 (d, J = 4.9 Hz, 2H), 7.26 (d,	
New Comments					(4-{((3,4,5-	J = 4.9 Hz, 2H), 7.25 (m, 1H), 7.03 (t, J = 7.4 Hz,	
Me CH	万		동	I	trimethoxy-benzyl)-	1H), 6.78 (d, J = 7.4 Hz, 1H), 6.75 (m, 1H), 6.61	ري ا
OMe					amino]-methyl}-	(s, 2H), 6.57 (m, 1H), 4.08 (bs, 2H), 3.86 (s, 6H),	
					pheyl}-acrylamide	3.83 (s, 3H), 3.50 (s, 2H), 3.47 (s, 2H), 2.21 (s,	
		\neg				3H).	
Me		_			N42-aminophenyl)-3-	¹ H-NMR (CDCl ₃), 8 (ppm): 7.74 (d, J = 15.4 Hz,	
MeO					(4-[(3,4,5-	1H), 7.50 (d, J = 7.4 Hz, 2H), 7.25 (m 3H), 7.06 (t,	
H	\exists		끙	I	trimethoxy-phenyl)-	J = 1.9 Hz, 1H), 6.82 (d, J = 7.4 Hz, 2H), 6.58 (d,	വ
MeO.					amino]-methyl}-	J = 15.4 Hz, 1H), 5.96 (s, 2H), 4.50 (s, 2H), 3.79	
OMe		-			phenyl}-acrylamide	(s, 6H), 3.78 (bs, 2H), 3.77 (s, 3H), 3.00 (s, 3H).	
					N42-Amino-phenyl)-	¹ H NMR: (DMSO-d ₆) δ (ppm): 9.4 (bs, 1H),	
ız					3-{4-[(6-methoxy-	7.60(d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87	
H5	万		끙	I	pyridin-3-ylamino)-	(d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-	വ
WeO / N			-		methy[]-phenyl}-	6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04	
					acrylamide	(m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).	
						1H NMR: (DMSO-d ₆) 8 (ppm): 9.41 (bs, 1H), 8.21	
\ \ \					N42-Amino-phenyl)-	(d, J = 8.5, 1H), 7.97 (dt, J = 7.7, 8.8 Hz, 2H),	
	_	Ę	Ę	ı	3-[4-(quinolin-2-	7.78 (dt, J = 7.1 Hz, 8.2 Hz, 1H), 7.61-7.53 (m,	u
,,,_/ z	•	=	5	=	ylsulfanylmethyl)-	5H), 7.40 (dd, J = 8.5 Hz, 7.6 Hz, 2H), 6.97-6.77	ი
,					phenyl]-acrylamide	(m, 4H), 6.6 (dt, J = 7.7 Hz, 7.5 Hz, 1H), 4.98 (bs,	
						2H), 4.65 (bs, 2H).	

EX.	Cpd.	×	>	λ	8	Name	Characterization	Schm
77	111	NH N	끙	용	I	N42-amino-phenyl)- 3-{4-{(pyridin-3- ylmethyl)-amino}- phenyl}-acrylamide	¹ H NMR: (DMSO-d6) 5 (ppm): 9.15 (s, 1H), 7.24 –7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).	9
78	112	NH NH	Z	동	工	N.(2-Amino-phenyl)- 3-(6-styrylamino- pyridin-3-yl)- acrylamide	¹ H NMR: (DMSO-d ₆) δ (ppm): 7.96 (d, J=9.1 Hz, 2H), 7.55 (d, J = 14.2 Hz, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.39-7.29 (m, 4H), 7.07-6.91 (m, 3H), 6.81-6.64 (m, 3H), 6.47-6.38 (m, 1H), 4.21 (bs, 2H).	7
79	113	N ₂ O	Z	Z	I	N42-amino-phenyl)-3-[2-4-nitro-benzylamino)-pyrimidin-5-yl]-acrylamide	¹ H NMR: (DMSO-d6) δ (ppm): 9.30 (s, 1H), 8.58 (bs, 2H), 8.36 (m, 1H), 8.20 (m, 2H), 7.58 (m, 2H), 7.28-7.42 (m, 2H), 6.52 –6.92 (m, 4H), 4.90 (s, 2H), 4.64 (d, J = 6 Hz, 2H).	7
80	114	MeO H	Z	НЭ	π '	N{5-[2-{2-Amino- phenylcarbamoyl- vinyl}-pyridin-2-yl}-4- methoxy-benzamide	¹ H NMR: (DMSO-d ₆) δ (ppm): 10.87 (bs, 1H), 9.45 (bs, 1H), 8.66 (bs, 1H), 8.33 (d, J = 7.4 Hz, 1H), 8.14-8.08 (m, 3H), 7.63 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 6.8 Hz, 2H), 6.97 (d, J = 12.3 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.7 Hz, 7.4Hz, 1H), 5.06 (bs, 2H), 3.88 (s, 3H)	7
81	115	. H ₂ N ₂ H	Z	z	Ξ	3-[2-4-amino-benzylamino-pyrimidin-5-yl]-N-{2-amino-phenyl}-acrylamide	¹ H NMR: (DMSO-d6) δ (ppm): 9.27 (s, 1H), 8.83 (s, 2H), 7.97 (t, J = 6 Hz, 1H), 7.37 (d, J = 15.9 Hz, 1H), 7.29 (d, J = 7.11 Hz, 1H), 6.96 (d, J = 8.24 Hz, 2 H), 6.88 (m, 1H), 6.70 (m, 2 H), 6.55 (m, 1H), 6.47 (d, J = 8.2 Hz, 2H), 4.90 (s, 4H), 4.34 (d, J = 6.0 Hz, 2H).	

\vdash	Cpd.	M	\	Y 2 R	æ	Name	Characterization	Schm
		MeO				N(2-aminophenyl)-3- [6-(3,4,5-trimethoxy-	¹ H-NMR (CDCI₃), 5 (ppm): 8.38 (bs, 1H), 7.49 (m, 1H), 7.42 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.41 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.10 (bs, 1H), 7.02	
	116	мео	z	ᆼ	I	benzylamino)-	(t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.0 Hz, 1H), 6.73	7,3
		OMe				pyriain-5-yij- acrylamide	(m 1n), 6.63 (m, 2n), 6.36 (q, J = 6.8 nz, 1n), 6.23 (d, J = 15.0 hz, 1h), 4.34 (s, 2h and bs,	
							2H), 3.84 (s, 3H), 3.81 (s, 6H).	
							¹ H NMR: (DMSO-d ₆) δ (ppm): 8.28 (bs, 1H), 7.98	
						M(2-Amino-phenyl)	(d, J = 9.6 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H),	
		\N \N		5		3-[6-(4-methyl-	7.38 (d, J = 7.7 Hz, IH), 7.29 (d, J = 7.9 Hz, ZH),	٦
		T	z	5	I	benzylamino}-	1.22 (d, J = 1.6 Hz, 2H), 1.08 (dt, J = 8.2 Hz, 1.7)	`
						pyrrum-3-yrg-	12, 111, 0:30 (u, J = 3:1 112, 211, 0:07 (t, J = 0:2 H-1 114, 147 (t, J = 0:4 H-1 114, 147 (t, J	
							2.53 (s, 3H).	
						N(2-amino-phenyl)-	¹ H NMR: (DMSO-d6) & (ppm): 9.27 (s. 1H). 8.54	
		Z	:	-	_ :	3-[2(4-methoxy-	(s, 2H), 8.12 (m, 1H), 7.30 (m, 4H), 6.53-6.91 (m,	١
	118	±	Z	z	I	benzylamino)-	(6H), 4.90 (s. 2H), 4.46 (d. J = 4.9 Hz. 2H), 3.7 (s.	`
						pyrimidin-5-yl]-	(HE)	
						acrylamide		
		,				M2-Amino-phenyll	¹ H NMR (20% CD ₃ 0D in CDCl ₃): III8.75 (s, 1H),	
		<u></u>				2.16.13 A dimethoxy		
	118b	MeO	z	공	エ	about avaidin 2 ull	_	9, 15
		- OMe				prierry/pyriant-3-yrg-	= 8.4 Hz, 1H), 6.89-6.83 (m, 3H), 3.96 (s, 3H),	
						acrylamide	3.91 (s, 3H).	

Table 3b

Ę.	Ex. Cpd. n	_	Name	Characterization	Scheme
53	87	0	87 0 2-4-methoxy-	¹ H-NMR (DMSO-d6) , δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz.	10
			٦.	1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5	
			6-carboxylic acid (2-	Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97	
			aminophenyl)-amide	(t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz. 1H).	
				4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).	
54	54 88	_	N42-aminophenyl}-3-[2-	N42-aminophenyl)-3-[2- 14-NMR (DMSO-d6), 8 (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz.	10
			(4-methoxy-	1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H).	
			benzyłamino)-quinolin-6-	benzylamino)-quinolin-6- 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7	
			yl]-acrylamide	Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t. J	
				= 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s. 3H).	

Table 3c

1	770	1 4		
ĭ	Cpa.	Мате	Characterization	Scheme
43	51	N(2-aninophenyl)-3-[6-(4-methoxy-	¹ H-NMR (CDCi₃) , δ (ppm): 7.60 (bs. 1H), 7.55 (bs. 1H), 7.43 (t. J = 7.7	က
		benzylamino)-pyridin-2-yl]-acrylamide	idin-2-yl]-acrylamide Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J =	
			7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41	
			(d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).	

Fable 3d

Cpd	W		Α	ZR	Name .	Characterization	Schm
347 492 H _{3C} O N N 35 CH CH	ir.	- - 5			N-(2-Amino-phenyl)-3- {4-[(4,6-dimethoxy- H pyrimidin-2-ylamino}- methyl]-phenyl}- acrylamide	¹ H-NMR (DMSO-46) , δ (ppm): 9.36 (bs, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.48 (s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 6.91 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 7.4, 7.7 Hz, 1H), 5.35 (s, 1H), 4.93 (bs, 2H), 4.46 (dd, J = 6.04 2H), 3.32 (s, 6H)	3,7
348 493 CI N N 15 CH CH	22	<u> </u>		<u> </u>	M2-Amino-phenyl)-3- {4-{(4-chloro-6- H methoxy-pyrimidin-2- ylamino)-methyl]- phenyl}-acrylamide	¹ H-NMR (DMSO-d6), δ (ppm): 9.37 (bs, 1H), 7.58-7.50 (m, 3H), 7.37-7.32 (m, 3 H), 6.94-6.83 (m, 2H), 6.75 (d J=8.0 Hz, 1H), 6.57 (t, J=7.5, 1H), 6.13 (bs, 1H), 4.48 (d, J=6.0, 2H), 3.84 (s, 3H)	3, 7
349 494 H _{3C} O H CH C	,,,,	<u>э</u>	()	Ŧ	CH CH H [4-(3,5-dimethoxy-benzylamino-phenyl]-acrylamide	¹ H-NMR (DMSO-d6), 8 (ppm): 9.38 (bs, 1H), 7.55-7.40 (m, 6H), 6.88-6.57 (m, 3 H), 6.35-6.32 (m, 1H), 5.73 (m, 3H), 4.94 (s, 2 H), 4.26 (s, 2H), 3.63 (s, 6H).	3, 7
350 495 O ₂ N H H O ₂ S CH C	H N NO2	СН С	()	<u> </u>	CH CH H benzylamino-phenyl)-3-	¹ H-NMR (DMSO-d6), δ (ppm): 9.38 (bs, 1H), 7.74 (bs, 3H), 7.61 (d, J=8.2 Hz, 2 H), 7.56-7.44 (m, 3H), 7.32 (d J=8.0 Hz, 1H), 6.91-6.85 (m, 2H), 6.73 (d, J=7.9 Hz, 1H), 6.66-6.56 (m, 1H), 4.93 (bs, 2H), 4.52 (bs, 2H).	3, 7

E	1_				
Schm	58	3, 7	37	28	3, 7
Characterization	¹ H-NMR (DMSO-d6), δ (ppm): 9.22 (bs, 1H), 7.52 (d, J=7.9 Hz, 2H), 7.44 (bs, 1H), 7.38 (bs, 3H), 7.28 (d J=6.9 Hz, 2H), 6.95-6.92 (m, 2H), 6.79 (d, J=8.2 Hz, 1H), 6.95-6.59 (m, 3H), 4.95 (bs, 2H), 4.45 (bs, 2H).	¹ H-NMR (DMSO-d6), 8 (ppm): 9.45 (bs, 1H), 8.01 (bs, 2H), 7.78-7.5 (m, 4H), 7.49-7.40 (m, 1H), 6.98 (dd, J=7.0, 8.2 Hz, 1H), 6.82 (d, J=7.0 Hz, 1H), 6.64 (dd, J=7.0, 7.6 Hz, 1H), 6.41 (bs, 2H), 5.17 (s, 2H), 3.81 (s, 6H), 3.64 (s, 3H).	M2-Amino-phenyll-3- H-NMR (DMSO-d6), δ (ppm): 9.22 (bs., 1H), 7.17 (d, 14(6,7-dimethoxy-3,4- J=8.2 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.93 (d, J=7.6 Hz, dihydro-1Hisoquinolin- IH), 6.85 (bs., 1H), 6.77 (bs., 1H), 6.60-6.53 (m, 3H), 6.43-2-yl-phenyll- 6.40 (m, 2H), 4.97 (bs., 2H), 4.43 (bs., 2H), 3.78 (s, 3H), acrylamide	¹ H-NMR (DMSO-d6), 6 (ppm): 10.77 (bs, 1H), 9.39 (bs, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.7 Hz, 2H), 7.37 (d, J=7.9 Hz, 2H), 7.26 (d, J=7.9, 2H), 7.10 (t, J=7.5 Hz, 2H), 7.00-6.83 (m, 4H), 6.78 (d, J=7.9 Hz, 1H), 6.61 (t, J=7.5 Hz, 1H), 5.98 (s, 1H), 5.32 (bs, 1H), 4.98 (bs, 2H), 4.32 (d, J=5.2 Hz, 2H), 3.98 (bs, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H).	¹ H-NMR (DMSO-d6), δ (ppm): 9.69 (bs, 1H), 8.04 (d, 1=8.3 Hz, 2H), 7.78 (d, 1=8.3 Hz, 2H), 7.58-7.55 (m, 2H), 7.06 (d, 1=6.2 Hz, 1H), 6.96 (d, 1=7.3 Hz, 1H), 6.90 (d, 1=7.0 Hz, 1H), 6.60 (bs, 1H), 5.81 (s, 2H), 4.34 (bs, 2H), 3.78 (s, 6H), 3.67 (s, 3H).
Name	M(2-Amino-phenyl)-3- [4(3-trifluoromethoxy- benzylamino-phenyl]- acrylamide	M(2-Amino-phenyl)-3- [4-(3,4,5-trimethoxy- phenoxymethyl)- phenyl]-acrylamide	M2-Amino-phenyl)-3- [4-(6,7-dimethoxy-3,4- dihydro-1 H-isoquinolin- 2-yl)-phenyll- acrylamide	M(2-Amino-phenyl)-3- (4-[[(1 H-indol-2- ylmethyl)(3,4,5- trimethoxy-phenyl)- amino]-methyl}- phenyl)-acrylamide	M.2-Amino-phenyil-3- [443,4,5-trimethoxy- phenylsulfanylmethyl}- phenyll-acrylamide
8	Ξ	I	Ξ	I.	I
2	공	끙	ᆼ		픙
Υ	HO HO	ਲ ਲ	сн сн	СН СН	СН СН
W	O R N Y	СН3 О Н3С-О Н3С-О	H ₃ C ₂ O	H ₃ C O H ₃	H ₃ C,O H ₃ C,O H ₃ C,O
Bas	496	497	498	499	200
Ex. Cpd	351	352 497	353	354	355 500

3-{4-((6-Acetyl-benzo[1,3]dioxol-5-27.9 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.9 Hz, 2H), 7.02-7.00 (m, 2H), 6.85 (d, J=7.5 Hz, phenyll-N42-amino-phenyll-acrylamide (6, J=7.2 Hz, 1H), 6.60 (bs, 1H), 6.36 (bs, 1H), phenyll-acrylamide (6.00 (d, J=2.2 Hz, 2H), 4.60 (bs, 2H), 2.50 (bs, 3H).
CH CH benzothiac-methyll-3- (m, 3H), 7.66-7.57 (m, 3H), 7.49 (d, J=7.5 Hz, 2H), 7.37-7.33 (m, 3H), 6.96-6.90 (m, 1H), 6.87 (d, J= 8.8 Hz, 1H), 6.80 (d, J=7.5 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.63 (t, J=7.5 Hz, 1H), 4.99 (bs, 2H), phenyll-acrylamide 4.64 (bs, 2H), 3.37 (s, 3H).
CH CH H phenylamino-methyll-3- (m, 3H), 7.47 (d, J=7.9 Hz, 2H), 7.39 (d, J=7.5 Hz, 1H), (4-{(f4-morpholin-4-yl-6.95 (d, J=8.3 Hz, 1H), 6.82 (bs, 1H), 6.77 (d, J=8.4 Hz, phenylamino)-methyll-2H), 6.66-6.56 (m, 3H), 5.91 (bs, 1H), 5.01 (bs, 2H), 4.30 (bs, 2H), 3.74 (bs, 4H), 2.93 (bs, 4H).
CH CH trifluoromethoxy-blenyll-3-blenyll-3-che

Schm	3, 33	3, 33	3, 33	55	14
Characterization	¹ H-NMR (DMSO-d₆) , δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.89-6.99 (m, 4H), 6.81 (d, J=7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.6 Hz, 1H), 6.56 (d, J = 8.2 Hz, 2H), 6.14 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 2.76 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H).	¹ H-NMR (DMSO-d₆) , 8 (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 5H), 7.40-7.52 (m, 7H), 7.27 (dd, J = 7.0, 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J=15.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 2H), 6.64 (dd, J = 7.6 Hz, 1H), 6.56 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.12 (d, J = 5.9 Hz, 2H).	¹ H-NMR (DMSO-d₆), δ (ppm): 9.50 (s, 1H), 8.81 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 15.7 Hz, 1H), 7.52 (d, J=8.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 6.96-7.05 (m, 2H), 6.81 (d, J = 8.0Hz, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.26 (m, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 6H), 3.56 (s, 3H).	¹ H-NMR (DMSO-d6) , δ (ppm): 9.50(s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.81-7.72 (s, 3H), 7.66 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.45-7.26 (m, 4H), 7.24-7.15 (m, 2H), 7.00-6.86 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 7.5 Hz, 1H), 5.45 (d, J = 16.8 Hz, 1H), 4.62 (bs, 1H), 4.25 (d, J = 12.9 Hz, 1H), 4.92 (d, J = 12.9 Hz, 1H), 1.91 (m, 2H), 1.28 (m, 1H), 0.90 (m, 1H), 0.72 (t, J = 7.5 Hz, 3H).	¹ H NMR: (Acetone-d ₆) δ (ppm): 9.47 (bs, 1H), 7.72-7.56 (m, 5H), 7.39 (d, J=7.4 Hz, 1H), 7.00-6.95 (m, 2H), 6.81 (d, J=6.9 Hz, 1H), 6.64 (t, J=7.1 Hz, 1H), 5.00 (bs, 2H).
Name	N-C-Amino-phenyll-3- [4-[(4:sopropyl- phenylamino-methyl]- phenyll-acrylamide	N{2-Amino-phenyl}-3- [4-{biphenyl-4- ylaminomethyl}- phenyll-acrylamide	N-C-Amino-phenyl)-3- (6-((3,4,5-trimethoxy- phenylamino)-methyl]- pyridin-3-yl)- acrylamide	M{2-Amino-phenyl}-3- (4-[[1-{3-benzyl-7- chloro-4-oxo-3,4- dihydro-quinazolin-2- yl)-ethylamino]-methyl}- phenyl}-acrylamide	CH CH (4-bromo-phenyl)-3-acrylamide
œ	I		I	Ξ	ᆼ
ZR	СН	н Н Н	z		끙
>	공	공	8	. 5	공
W	H ₃ C CH ₃	IX S	MeO MeO MeO	N N N N N N N N N N N N N N N N N N N	Br
Pd	510	511	512	514	516
EX.	365	366	367 !	369	371

<u></u>	0	Τ	I	1	Υ	T
Schm	1,7, 1	58	59	29	m	m
Characterization	¹ H NMR: (CD ₃ OD) 8 (ppm): 7.61 (d, J=15.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.25 (d, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.81 (t, J=7.0 Hz, 1H), 6.76 (s, 1H) 6.70 (d, J=8.4 Hz, 2H), 6.92 (d, J=15.4 Hz, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.77 (s, 3H)	1H NMR (DMSO-d6) δ (ppm): 9.24 (s, 1H), 8.00 1(d, J=12Hz, 1H); 7.80 (d, J=12Hz, 1H), 7.40-7.70 (m, 7H), 6.80-7.00 (m, 2H), 6.70 (d, J = 12Hz, 1H), 6.20 (s, 2H), 4.50 (m, 1H), 3.70 (s, 6H), 3.50 (s, 3H), 1.50 (d, 3H).	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.41 (s, 1H), 8.00 (t, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.77-7.56 (m, 3H), 7.52-7.32 (m, 3H), 7.00 (d, J = 15.8 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 5.00 (s, 2H), 4.03 (s, 2H),	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm); 9.71 (s, 1H), 9.43 (s, 1H), AB system ($\delta_A = 8.05$, $\delta_B = 7.75$, $J = 7.9$ Hz, 4H), 7.62 (d, $J = 15.8$ Hz, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.05-6.88 (m, 3H), 6.78 (t, $J = 7.9$ Hz, 2H), 6.65-6.55 (m, 2H), 4.96 and 4.92 (2s, 4H).	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.29 (s, 1H), 8.32 (d, J = 4.9 Hz, 2H), 8.24 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.48 (d, J = 15.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.26 (bs, 2H), 6.96 (t, J = 6.9 Hz, 1H), 6.80 (dd, J = 1.1, 7.7 Hz, 1H), 6.69-6.61 (m, 4H), 5.00 (s, 2H), 3.52 (bs, 4H),	¹ H NWR (300 MHz, CD ₃ OD) 8 (ppm): 8.12 (s, 1H), 8.08 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 15.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 15.4 Hz, 1H), 6.65 (s, 1H), 4.90 (s, 5H), 3.50-3.45 (m, 4H), 3.30 (d, J = 1.3 Hz, 1H).
Name	CH CH CH (2,4,5-trimethoxy-benzylamino)-benzamide	CH CH CH trimethoxy-phenyll-3-phenylamino-phenyll-3.4,5-phenylamino-ethyll-phenyll-acrylamide	C CH H (9H-fluoren-2-yl)- acrylamide	CH CH (2-42-amino-phenyl)-4-phenylcarbamoyl)-vinyll-benzamide	M{2-Amino-phenyl}-3- {6-{2-Apyrimidin-2- ylamino}-ethylamino}- pyridin-3-yl}- acrylamide	N(2-Amino-phenyl)-3- (6-{2-{thiazol-2- N CH H ylamino}-ethylamino}- pyridin-3-yl}- acrylamide
8	끙	퓽	Ξ	I		±
7	픙	늉	픙	- 	H H C	丟
\	풍	용	ပ	픙	z	z
М	MeO OMe OMe	MeO OMe CH ₃ MeO HeO HE	Y-7-4 Y	HN S N	IX XII	NI NI
Ex. Cpd	517	518	519	520	521	522
ŭ	372	373	374	375	376 521	377

_	T	<u> </u>				
Schm	3, 33,	m	က	3, 33,	3, 33, 58	3, 33
Characterization	¹ H-NMR (CD₃OD) , δ (ppm): 7.83 (d, J = 15.6 Hz, 1H), 7.67 (d, J = 7.8 Hz, 2H), 7.62-7.58 (m, 2H), 7.53-7.51 (m, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 15.6 Hz, 1H), 1, 4.99 (bs, 9H), 4.84 (bs, 2H), 4.22 (t, J = 6.5 Hz, 2H), 4.05 (s, 4H), 3.85 (s, 6H), 3.76 (s, 3H), 3.57-3.50 (m, 4H).	¹ H-NMR (DMSO-d₆) , δ (ppm): 9.32 (s, 1H), 9.26 (s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.32 (d J=7.7 Hz), 7.10 (t, J = 7.6 Hz, 1H), 6.91 (t, J=7.6 Hz, 1H), 6.75 (m, 3H), 6.59 (m, 4H), 4.98 (bs, 2H), 4.46 (d, J=5.8 Hz, 2H).	¹ H-NMR (DMSO-d ₆), δ (ppm): 9.25 (s, 1H), 8.18 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.30 (m, 2H), 7.00 (m, 2H), 6.92 (m, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.60 (m, 3H), 4.92 (s, 2H), 4.73 (q, J = 8.8 Hz, 2H), 4.52 (d, J = 5.8 Hz, 2H).		¹ H-NMR (DMSO-d ₆ , δ (ppm): 9.43 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.00-6.88 (m, 2H), 6.85-6.79 (m, 2H), 6.63 (t, J = 7.6 Hz, 1H), 6.44-6.30 (m, 3H), 4.99 (bs, 2H), 4.30 (d, J = 5.5 Hz, 2H), 2.87 (bs, 4H), 2.55 (m, 4H), 2.27 (s, 3H).	
Name	M:2-Amino-phenyl}-3- (4-(((2-morpholin-4-yl- ethyl)K3,4,5- trimethoxy-phenyl}- amino]-methyl}- phenyl}-acrylamide	N(2-Amino-phenyl)-3- [6(3-hydroxy- benzylamino)-pyridin-3- yl]-acrylamide	N42-Amino-phenyl)-3- (6-13-(2,2,2-trifluoro- N CH H ethoxy)-benzylaminoj- pyridir-3-yl)- acrylamide	M2-Amino-phenyl)-3- (4-([3-hydroxy-4-(4- methyl-piperazin-1-yl)- phenylamino]-methyll- phenyl)-acrylamide	M2-Amino-phenyl)-3- (4-[[3-fluoro-4-(4- methyl-piperazin-1-yl)- phenylamino]-methyl)- phenyl}-acrylamide	M-(2-Amino-phenyl)-3- H (4-f(3-hydroxy- phenylamino)-methyll- phenyll-acrylamide
2	I	Ξ	I	Н	Ŧ	· エ
YZR			퓽	CH CH	픙	ᆼ
>	СН СН	N CH	z	용	Э	СН СН
A	J-N-N-OME MGO OME	φ XI XI	O CF ₃	Me-N NH CH CH CH	HN N N N N N N N N N N N N N N N N N N	H Y HO
Cpd	523	524	525	526	527	528
Ex.	378	379	380	381	382	383

Ex. Cpd	Pd	W	>	7	R	Characterization	Cohm
384	529	DF N SE	당		M{2-Amino-phenyl}-3- {4-[(4-trifluoromethyl- Pyrimidin-2-ylamino)- methyl}-phenyl}- acrylamide	¹ H-NMR (CD₃OD), δ (ppm): 7.73 (d, J = 16.0 Hz, 1H); 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.03 (dt, J = 7.7, 1.4 Hz, 1H), 6.89 (d, J = 1.1 Hz, 1H), 6.85 (m, 1H), 6.73 (dt, J = 7.7, 1.1 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H), 4.87 (bs, 2H), 4.62 (s, 2H)	, a
385 5	530	J. N. OH	용	СН	M(2-Amino-phenyl}-3- (4-{(3-hydroxymethyl- phenylamino)-methyl}- phenyll-acrylamide	¹ H-NMR (DMSO-d ₆), δ (ppm): 9.90 (s, 1H), 7.58 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H); 7.37 (d, J = 8.0 Hz, 1H), 7.11 (m, 1H), 7.00 (m, 3H), 6.85 (d, J = 15.4 Hz, 1H), 6.63 (s, 1H), 6.51 (d, J = 7.4, Hz, 1H), 6.46 (d, J = 7.7 Hz, 1H), 4.35 (s, 2H), 4.32 (s, 2H).	3, 33
386 5	531	IX X	СН		M(2-Amino-phenyl)-3- {4-t(4-pyridin-4- ylmethyl-phenylamino}- methyl]-phenyl}- acrylamide	14-NMR (DMSO-de), 5 (ppm): 9.66 (s, 1H), 8.46 (d, J = N42-Amino-phenyl)-3- 4.7 Hz, 2H); 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 15.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4.7 Hz, 2H), ylmethyl-phenylamino)- 7.00 (d, J = 15.7 Hz, 1H), 6.92 (d, J = 6.9 Hz, 2H), 6.90 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 6.58 (m, 2H), 6.52 (d, J = acrylamide 6.9, Hz, 2H), 6.10 (bs, 1H), 4.26 (bs, 2H), 3.80 (s, 2H), 2.08 (d, J = 1.9 Hz, 2H).	3, 33
387 5	532	IN NO	СН	표	M{2-Amino-phenyl}-3- {4-{(3-cyano- phenylamino}-methyl}- phenyl}-acrylamide	H-NMR (DMSO-d ₆), δ (ppm): 9.38 (s, 1H), 7.58 (d, J = 7.7 Hz, 2H); 7.54 (d, J = 15.9 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.92-6.83 (m, 5H), 6.75 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 4.95 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).	3, 33
388	533	NHAC	<u> </u>		3-(4-[[3-(Acetylamino-methyl)-phenylamino]-H methyll-phenyl)-N-(2-amino-phenyl)-acrylamide	Z, 4,	88 6

_	· · · · · · · · · · · · · · · · · · ·			<u> </u>	
Schm	3, 33	3, 33	м	m	1, 3, 33
Characterization	¹ H-NMR (DMSO-d₆) , 6 (ppm): 9.37 (bs, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.7Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67 (6.55 (m, 4H), 5.84 (t, J = 5.8 Hz, 1H), 4.94 (bs, 2H), 4.22 (d, J = 5.8 Hz, 2H).	¹ H-NMR (DMSO-d₆) , δ (ppm): 9.39 (bs, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 15.7 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.1 Hz, 1H), 6.97-6.89 (m, 2H), 6.87 (d, J = 15.7 Hz, 1H), 6.75 (dd, J = 1.4, 8.0 Hz, 1H), 6.60-6.55 (m, 4H), 4.95 (bs, 2H), 4.33 (d, J = 6.0 Hz, 2H).	¹ H-NMR (CDC I ₃), 6 (ppm): 8.12 (bs, 1H), 7.64 (d, J = 14.2 Hz, 1H), 7.42 (bs, 4H), 7.23 (bs, 2H), 6.97 (d, J = 14.2 Hz, 1H), 6.94-6.82 (m, 4H), 6.70 (s, 2H), 4.11 (bs, 2H), 3.87 (s, 6H), 3.84 (s, 3H).	¹ H-NMR (DMSO-d ₆), 6 (ppm): 8.49 (s, 1H), 7.58 (d, J = 15.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (m, 4H), 7.00 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 5.0 Hz, 2H), 6.69 (d, J = 5.0 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 6.53 (bs, 2H), 6.47 (s, 2H), 3.85 (s, 3H), 3.63 (s, 6H).	¹ H-NMR (CD₃OD/CDCl₃), δ (ppm): 7.61 (d, J = 15.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 (dd, J = 8.0 Hz, 2H), 7.12 (d, J = 15.7 Hz, 1H), 7.10 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.83-6.66 (m, 4H), 3.93 (bs, all NH signals).
Name	N-(2-Amino-phenyl)-3- (4-{(4-nitro-3- trifluoromethyl- phenylamino-methyl)- phenyll-acrylamide	N-(2-Amino-phenyl)-3- (4-((3,5-dichloro- phenylamino)-methyll- phenyl)-acrylamide	N(2-Amino-phenyl)-3- (4-[2-(3,4,5- trimethoxy-phenyl)- vinyl]-phenyl)- acrylamide	M(2-Amino-phenyl)-3- [4-[2-(3,4,5- trimethoxy-phenyl)- vinyl]-phenyl)- acrylamide	N-(2-Amino-phenyl)-3- (4-[(3-sulfamoyl- phenylamino)-methyl]- phenyl)-acrylamide
8	I	Ŧ	I	Ξ	Ŧ
YZR	СН	CH	СН	ᆼ	끙
Υ	СН СН	СН	сн сн	НО НО	В но
W	O ₂ N H Y	D IN D	MeO MeO MeO	MeO OMe	SO ₂ NH ₂
B	534	535	536	537	538
Ex. Cpd	388	390 (391	392	393

5	~	~		T		Т——
Schm	3, 33,	3, 32	3, 33	3, 33	3, 33	3, 33
Characterization	¹ H-NMR (CDCI₃), 5 (ppm): 8.34 (bs, 1H), 7.64 (d, J = 15.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.34 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 15.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.04 (m, 2H), 6.74 (m, 4H), 4.85 (bs, 1H), 4.30 (d, J = 4.4 Hz, 2H), 3.69 (t, J = 4.4 Hz, 4H), 2.99 (t, J = 5.8 Hz, 2H), 2.40 (bs, 6H), 1.59 (t, J = 4.4 Hz, 2H).	¹ H-NMR (CDCl ₃), δ (ppm): 8.53 (s, 1H), 7.72 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.33 (m, 1H), 7.16 (d, J = 7.7 Hz, 2H), 7.07 (m, 1H), 6.79 (m, 2H), 6.69 (d, J = 15.6 Hz, 1H), 6.41 (s, 2H), 4.04 (bs, 2H), 3.91 (s, 3H), 3.85 (s, 6H), 2.94 (m, 4H).	"H-NMR (DMSO-d ₆), δ (ppm): 9.35 (s, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.6 Hz, 2H), 6.58 (m, 1H), 6.52 (d, J = 8.6 Hz, 2H), 5.84 (t, J = 5.5 Hz, 1H), 4.23 (d, J = 5.5 Hz, 2H), 3.61 (s, 3H).	¹ H-NMR (CDCl ₃), 6 (ppm): 8.48 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.27 (m, 5H), 6.97 (t, J = 7.5 Hz, 1H), 6.70 (m, 3H), 6.59 (d, J = 15.4 Hz, 1H), 6.25 (s, 1H), 6.12 (d, J = 7.1 Hz, 1H), 4.23 (s, 2H), 3.93 (bs, 3H), 3.75 (s, 3H), 3.73 (s, 3H).	Mt2-Amino-phenyl)-3- ¹ H-NMR (CD₃OD), δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), (4-[[3-1]H-tetrazol-5-yl)-7.60 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.33 (m, phenylaminol-methyl)- 3H), 7.27 (m, 3H), 7.20 (m, 1H), 6.84 (m, 2H), 5.48 (bs, phenyl)-acrylamide 5H), 4.46 (s, 2H).	¹ H-NMR (CD ₃ OD), 8 (ppm); 7.75 (d, J = 15.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 7.20 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 15.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 5.48 (bs, 5H), 4.39 (s, 2H), 4.16 (s, 2H)
Name	M{2-Amino-phenyl}-3- (4-{13-(3-morpholin-4- y-propylsulfamoyl)- phenylamino]-methyl}- phenyl}-acrylamide	M-(2-43,4,5- (4-[2-(3,4,5- H trimethoxy-phenyl)- ethyll-phenyl)- acrylamide	N-(2-Amino-phenyl)-3- (4-[(4-methoxy- phenylamino)-methyl]- phenyl}-acrylamide	N-(2-Amino-phenyl)-3- [4-[(3,4-dimethoxy- phenylamino)-methyl]- phenyl)-acrylamide	N. CAmino-phenyl. 3- (4-([3.4] H. tetrazol. 5-yl.)- phenylamino]-methyl. phenyl. acrylamide	N-(2-Amino-phenyl)-3- (4-([4-(1 H-tetrazol-5- ylmethyl)- phenylaminol-methyl)- phenyl-acrylamide
~	Ŧ	I			I	E E
7	공	공	끙	- - -		
>	ਲ ਲ	CH CH	н Н С	СН СН	СН СН	СН
M	N S S O N H	MeO OMe	H ₃ C, ONI	CH3 O-CH3 N-5- N-5-	HN	IN NI N
B	539	540	541	542	543	544
Ex. Cpd	394	395	396	397 5	398 5	399 5

Ex. Cpd W			YZR	1 2	Name	Characterization	Schm
Τ:	·				M2-Amino-phenyll-3-	¹ H NMR (300 MHz, DMSO·d ₆) δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 15.6 Hz, 1H), 7.45	
jr.	jr.	- - - - - - - - -	_ <u></u>		CH CH H [4-((4-bromo-	7	3, 33
Ž,	, in	·			phenyll-acrylamide	1H), 6.80 (d, J = 8.0 Hz, 1H), 6.66-6.57 (m, 4H), 4.99 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H).	
TZ	T 2			ı	M2-Amino-ohenvl)-3-	¹ H NMR (300 MHz, DMSO-de) 8 (ppm): 9.36 (s, 1H),	
× × × × × × × × × × × × × × × × × × ×							-
401 546 CH CH F					h phenylamino)-methyl]-	Ē	3, 33
					phenyl}-acrylamide	ZH), 6.86 (d, J = 13.8 HZ, 1H), 6.74 (d, J = 6.2 HZ, ZH), 6.666.54 (m, 4H), 4.93 (bs, 2H), 4.30 (d, J = 5.3 HZ, 2H).	
						¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.36 (s, 1H),	
Ι	Ι				M2-Amino-ohenvll-3-	7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.39	
\2\N\\	75					(d, J = 8.0 Hz, 2H), 7.35 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H),	
402 547 (CH CH H	H HO HO CH CH H	<u> </u>	Ϊ Ξ	-1-		6.92 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.75	3, 33
					phenyl-acrylamide	(d, J = 7.7 Hz, 1H), 6.57 (t, J = 8.0 Hz, 1H), 6.52 (t, J = 1.0 Hz)	
-	-	-				6.0 Hz, 1H), 6.42 (d, J = 8.5 Hz, 2H), 4.94 (bs, 2H), 4.28	
			+			(d, J = 6.0 Hz, 2H).	
T:	I:				M2-Amino-phenyll-3-	¹ H NMR (300 MHz, DMSO-d ₆) 8 (ppm): 9.40 (s, 1H),	
s S	W. W.				(4-1/3-indo-	7.57 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 15.6 Hz, 1H), 7.40	
403 548 CH CH H	H HO HO	프 공 공	工厂	_	CH CH H Chenylamino\methyll.	(d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 6.92 (m, 3H),	3, 33
>	>				phenyll-acrylamide	6.84 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.60-6.50 (m, 3H),	
			+-			14 NMR (300 MHz. DMSO-ds) & (50m): 9.42 (5. 1H).	
ر بر	,,, I Z				M2-Amino-phenyl)-3-	7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.46	
	~~				(4-{[3-{2-hydroxy-	(d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.03-6.98 (m,	
404 549 CH CH H	HO HO	공 공	ĭ			2H), 6.91 (d, J = 15.3 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H),	3, 33
-	-				methyl}-phenyl}-	6.64 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 5.9 Hz, 1H), 6.28	
	-				acrylamide	6.22 (m, 3H), 4.99 (bs, 3H), 4.61 (s, 2H), 4.34 (d, J = 5.0	
						Hz, 2H) 4.28 (d, J = 5.0 Hz, 2H).	

E	8	83	22	83	82
Schm	3, 33	3, 33	3, 33	3, 33	3, 33
Characterization	¹ H NMR (300 MHz, CD ₃ 0D) δ (ppm): 7.64 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (s, 3H).	¹ H NMR (300 MHz, DMSO-46) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.60-6.54 (m, 3H), 6.39 (t, J = 5.7 Hz, 1H), 4.93 (bs, 2H), 4.29 (d, J = 6.1 Hz, 2H), 2.32 (s, 3H).		¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.37 (s, 1H), 8.25 (m, 1H), 7.76 (m, 1H), 7.57 (m, 2H), 7.47 (m, 4H), 7.33 (d, J = 7.0 Hz, 1H), 7.17 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 5.3 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 4.90 (s, 2H), 4.54 (d, J = 5.3 Hz, 2H).	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.39 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.02 (q, J = 7.6 Hz, 1H), 6.90 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (m, 1H), 6.40 (d, J = 8.2 Hz, 1H), 6.29 (m, 2H), 4.90 (s, 1H), 4.29 (bs. 2H), 4.02 (s, 2H).
Name	M2-Amino-phenyl)-3- {4-((3-methylsulfanyl- phenylamino}-methyl}- phenyl}-acrylamide	N{2-Amino-phenyl}-3- {4-{(4-methylsulfanyl- phenylaminol-methyl]- phenyl}-acrylamide	N42-Amino-phenyl)-3- {4-[(5-bromo-pyridin-2- ylamino)-methyl]- phenyl)-acrylamide	N(2-Amino-phenyl)-3- [4-(naphthalen-1- ylaminomethyl)- phenyl]-acrylamide	M2-Amino-phenyll-3- [4-[(3-fluoro- phenylaminol-methyl]- phenyll-acrylamide
æ		I	Ŧ	I	I
YZR	СН СН	СН	ж	сн сн	сн сн
\	СН	CH.	동	Б	СН
W	SMe	MeS H	J. H. J.	IN	TZ TZ
Pd	555	556	557	558	559
Ex. Cpd	410	411	412	413	414

Cohm	09	Schm	3, 33	Schm	33	33
2		Sc		Scl		3, 33
Characterization	¹ H-NMR (CD(7.63 (d, J = 1 (m, 2H), 6.68-(s, 2H), 3.86 (3H).	Characterization	¹ H NMR (300 MHz, CDCl ₃) & (ppm): 9.22 (s, 1H), 9.11 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 15.8 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 15.8 Hz, 1H), 6.78 (t, J = 7.9 Hz, 1H), 6.23 (t, J = 7.9 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 6.09 (t, J = 6.2 Hz, 1H), 5.89 (s, 2H), 4.77 (bs, 2H), 4.27 (d, J = 5.7 Hz, 2H), 5.89 (s, 6H), 5.76 (s, 3H)	Characterization	¹ H NMR (300 MHz, CDC! ₃) δ (ppm): 8.25 (s, 1H), 7.74 (d, J = 15.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 4.36 (s, 2H), 4.18 (bs, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H)	IH NMR (300 MHz, CDCI ₃) & (ppm): 8.58 (s, 142-Amino-phenyl)-3.[4{(4-1H), 7.66 (d, J = 15.4 Hz, 1H), 7.33-7.28 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 7.04 (t, J = 7.0 trimethoxy-phenylamino)- Hz, 1H), 6.77-6.70 (m, 4H), 6.64 (d, J = 15.4 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 5.90 (s, 2H), methyl)-phenyl3-acrylamide 4.27 (s, 2H), 4.25 (s, 2H), 4.08 (bs, 4H), 3.82 (s, 6H).
Name	N42-Amino-phenyl)-3-{3,5-dimethoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide	Name	N-(2-Amino-3-hydroxy- phenyl)-3-(4-[(3,4,5- trimethoxy-phenylamino)- methyl]-phenyl}- acrylamide	Name	1)-3-{4- y- thyl]- le	M{2-Amino-phenyl}-3-[4-(4-methoxy-3-[(3,4,5-hermethoxy-phenylamino)-methyl]-phenylamino}-methyl}-phenyl]-acrylamide
8		YZR	NH OH	~	I	H H
7	F Z	Σ	- Ā Ā	7	СН СН	СН
>	<u> </u>		Z-()	>	СН	СН СН
W	MeO H Nao OMe OMe	M	MeO OMe	M	MeO OMe H 255	OMe HN OMe MeO
B	560	Dd C	561	pdo	299	563
EX.	415 560	Ä	416 561	EX.	417 562	418 5

Schm	3, 33	Schm	3, 33	3, 33	Schm	3, 33
Characterization	¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 7.64 (d, J = 15.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.31-7.24 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 15.4 Hz, 1H), 5.84 (s, 2H), 4.27 (s, 2H), 4.00 (bs, 6H), 3.71 (s, 6H), 3.68 (s, 3H).	laracterization	¹ H-NMR (DMSO-d₆) , δ (ppm): 9.38 (bs, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 15.4Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 8.3 Hz, 1H), 6.94-6.89 (m, 2H), 6.81 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.43-6.38 (m, 2H), 4.94 (bs, 2H), 4.30 (d, J = 5.7 Hz, 2H). 2.28 (s, 3H).	M2-Amino-phenyl)-3-{4-[(4-7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 15.8Hz, methylsulfanyl-3-{4-[(4-7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 trifluoromethyl- Hz, 1H), 7.33 (d, J = 6.2 Hz, 1H), 6.96-6.90 phenylamino)-methyl- (m, 4H), 6.82 (d, J = 15.8Hz, 1H), 6.79-6.74 phenyll-acrylamide (m, 1H), 6.58 (t, J = 7.5 Hz, 1H), 4.95 (bs, 2H), 4.35 (d, J = 6.2 Hz, 2H). 2.35 (s, 3H).	Characterization	**H-NMR (DMSO-de,), & (ppm): 9.50 (s, 1H), 8.09 (s, 1H), 7.80 (d, J = 15.4 Hz, 1H), 7.81 (s, 2H), 7.34 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 15.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.26 (t, J = 6.2 Hz, 1H), 5.90 (s, 2H), 4.96 (bs, 2H), 4.39 (d, J = 5.7 Hz, 2H), 3.66 (s, 6H), 3.51 (s, 3H).
Name	N(2,3-Diamino-phenyl)-3- {4-[(3,4,5-trimethoxy- phenylamino)-methyl]- phenyl}-acrylamide	Name	N{2-Amino-phenyl}-3-{4-[(3- fluoro-4-methylsulfanyl- phenylamino)-methyl}- phenyl}-acrylamide		Name	M{2-Amino-phenyl}-3-{3- nitro-4-[(3,4,5-trimethoxy- phenylamino}-methyl]- phenyl}-acrylamide
R		R	I	Ι	4	0 0
7	ž ž	7	н 	СН СН	7	Į, Į,
Υ	¥_<	Υ	<u> </u>	G	>	<u></u>
M	MeO H	W	H ₃ C-S	H ₃ C S	M	Meo H Neo Meo
PdO	564	· pdɔ	565	566	Cpd	567
Ĕ.	419	EX.	420	421	Ex.	422

Schm	3, 33	3, 15, 33	m 0
S	, κ	ี้ พี้	33,
Characterization	¹ H-NMR (DMSO-d₆) , δ (ppm): 9.29 (s, 1H), 7.72 (d, J = 15.4 Hz, 1H), 7.33 (m, 2H), 6.90 (1H); 6.71 (2H), 6.62 (3H), 5.97 (1H), 5.87 (2H), 5.49 (2H), 4.96 (2H), 4.10 (2H), 3.51 (3H).	LRMS: calc: 375.4, found: 376.4	¹ H-NMR (DMSO-d6), δ (ppm): 9.64 (bs, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.60 (d, J=14.0 Hz, 1H), 7.50 (d, J=7.9 Hz, 2H), 6.90 (d, J=15.8 Hz, 1H), 6.15 (d, J=4.0 Hz, 1H), 5.95 (s, 2H), 5.82 (s, 1H), 4.89 (bs, 2H), 4.33 (d, J=5.7 Hz, 2H), 3.71 (s, 6H),
Name	M(2-Amino-phenyl)-3-{3-amino-4-[(3,4,5-fr)] (1H); 6.71 (2H) , 6.62 (2H) , 5.49 (2H) , 4.96 methyl]-phenyl]-acrylamide $\frac{^{1}\text{H-NMR} (DMSO-de_J), 8}{(1,1,1,2,2,3,4,5)}$	N(2-Amino-phenyl)-3-[6- (3,4-dimethoxy-phenyl)- pyridin-3-yl]-acrylamide	N{4-Amino-thiophen-3-yl}-3-{4-[(4-morpholin-4-yl-phenylamino)-methyl]-phenyl}-acrylamide
W Y Z R	MeO H ₂ N NH ₂ NH ₂ NH ₂ OMe	H ₃ C ₂ O	H ₂ C H ₃ C H ₃ C H ₃ C H ₃ C-O
B S	568	569	920
Ľ.	423	424	425

Example 85

N-(2-Amino-phenyl)-4-(1H-benzimidazol-2-ylsulfanylmethyl)-benzamide (compound 126)

Step 1: 4-(1H-Benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (compound 122)

[0211] Following the procedure described in Example 47, step 2, but using **119** and substituting **121** for **63**, the title compound **122** was obtained in 95% yield. LRMS = 299.1 (M+1).

Step 2: N(2-Amino-phenyl)-4-(1H-benzimidazol-2-ylsulfanylmethyl)-benzamide (126)

[0212] Following the procedure described in Example 1, steps 4 and 5, but substituting 122 for 6, the title compound 126 was obtained in 62% yield. 1 H NMR: (DMSO-d₆) δ (ppm): 9.57 (s, 1H), 7.89 (d, J= 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.53 (bs, 2H), 7.36 (bs, 2H), 7.14-7.08 (m, 3H), 6.94 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 6.56 (t, J = 8.0 Hz, 1H), 4.87 (bs, 2H), 4.62 (s, 2H).

Example 87

N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound 128)

Step 1: 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (122)

[0213] Following the procedure described in Example 47, step 2, but using **120** and substituting **121** for **63**, the title compound **122** was obtained in 45% yield. LRMS = 331.0 (M+1).

Step 2: 4-[6-(2-Morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyll-benzoic acid methyl ester (compound 124)

[0214] To a solution of 4(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester 122 (800 mg, 2.42 mmol), in DMF (24 mL), were added successively solid 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol), K_2CO_3 (611 mg, 5.08 mmol), Nal (363 mg, 2.42 mmol), E_3N (370 μ L, 2.66 mmol) and tetrabutylammonium iodide (894 mg, 2.42 mmol), The mixture was stirred at 120°C for 24h and more 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol) was added. The mixture was stirred for 8h at 120°C and the solvent was removed *in vacuo*. The resulting black syrup was partitioned between H_2O and E_3N and E_3N and E_3N washed with HCl 1N and saturated aqueous E_3N and E_3N and concentrated. Purification by flash chromatography (MeOH/CHCl3: 5:95 to 10:90) afforded 48 mg (4% yield) of 124 as a light yellow oil. LRMS = 444.1 (M+1). Step 3: N_3N and compound 128)

[0215] Following the procedure described in Example 1, steps 4 and 5, but substituting 124 for 6, the title compound 128 was obtained in 76% yield. 1 H NMR: (Acetone- $_{6}$) δ (ppm): 9.06 (bs, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.02-6.97 (m, 1H), 6.87-6.82 (m, 2H), 6.66 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.63 (s, 2H), 3.64-3.60 (m, 4H), 3.25 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.54-2.42 (m, 4H).

Example 88

N-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (compound 131)

Step 1: 2-(4-Bromo-benzylsulfanyl)-quinoline (compound 130)

[0216] Following the procedure described in Example 47, step 2, but substituting 129 for 63, the title compound 130 was obtained in 89% yield. LRMS = 332.0 (M+1).

Step 2: N(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (131)

[0217] Following the procedure described in Example 40, step 2, but substituting 129 for 42, the title compound 131 was obtained in 70% yield. 1 H NMR: (DMSO-d₆) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).

Example 89

N-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (compound 134)

Step 1: 4(Pyrimidin-2-ylaminomethyl)-benzoic acid methyl ester (compound 133)

[0218] Following the procedure described in Example 47, step 2, but substituting 132 for 63, the title compound 133 was obtained in 76% yield. LRMS = 244.2 (M+1).

Step 2: N(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (134)

[0219] Following the procedure described in Example 1, steps 4 and 5, but substituting 129 for 6, the title compound 134 was obtained in 91% yield. 1 H NMR: (DMSO-d₆) δ (ppm): 9.6 (bs, 1H), 8.32 (d, J = 4.9 Hz, 2H), 7.97 (dt, J = 9.9 Hz, 7.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47, (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).

Example 90

N-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl]-benzamide (compound 139)

Step 1: [2-(4-lodo-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (compound 135)

[0220] To a solution of di-tert-butyldicarbonate (39 g, 181 mmol) in THF (139 mL) placed in a water bath, was added 1,2-phenylenediamine (15 g, 139 mmol) and DMAP (1.7 g, 14 mmol). The mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was partitioned between EtOAc and water. The organic layer was washed with HCl 1 N and then with aqueous saturated NaHCO₃. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated affording the compound (18.9 g, 65% yield) as a light beige powder. LRMS = $209.1 \, (M+1)$.

[0221] To a solution of 4-iodobenzoic acid (8.0 g, 32.3 mmol) in DMF (65 mL) at r.t., were successively added 1-[3-(dimethylamino)propyl]-3-ethylcabodiimide hydrochloride (8.0 g, 41.9 mmol) and 1-hydroxybenzotriazole (5.2 g, 38.7 mmol). The mixture was stirred for 1 h and a solution of (2-amino-phenyl)-carbamic acid *tert*-butyl ester (6.3 g, 30.2 mmol) in DMF (20 mL) was added to the mixture *via* cannula, followed by triethylamine (5.9 mL, 4.9 mmol). The mixture was stirred for 16 h

and the solvent was removed in vacuo. The crude material was partitioned between chloroform and water. The organic layer was washed with aqueous saturated NaHCO₃, dried over MgSO₄ and concentrated to a light brown syrup which was crystallized in hot EtOAc or Et₂O, yielding **135** (9.3 g, 70% yield) as a white solid. LRMS = $461.0 \, (M+Na^+)$.

Step 2: N[2-tert-butoxycarbonylamino-phenyl)-terephtalamic acid methyl ester (compound 136)

[0222] Following the procedure described in Example 40, step 2, but substituting 135 for 42, the title compound 136 was obtained in 95% yield. LRMS = 393.1 (M+Na⁺).

Step 3: [2(4-Hydroxymethyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (137)

[0223] To a solution of 136 (7.5g, 20.6 mmol) in THF (40 mL), cooled down to -20° C under N₂, was added a 1M solution of DIBAL-H (122 mL, 122 mmol) in toluene. After stirring for 18 h. at r.t., the mixture was cooled down to 0°C and carefully quenched by a dropwise addition of H₂O (10 mL) and of 2N NaOH (5 mL). The aluminum salts were allowed to decant and the supernatant was removed. The organic layer was washed with H₂O, 1 N HCl (6 times), satd. aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated (2.04 g, 43%). Purification of the crude material by flash chromatography (EtOAc/hexanes 50:50 to 70:30) afforded 137 (1.14 g, 16% yield) as a solid foam. LRMS = 365.2 (M+Na⁺).

Step 4: {2-[4-(1-Methyl-imidazol-2-ylsulfanylmethyl)-benzoylaminol-phenyl)-carbamic acid tert-butyl ester (compound 138)

[0224] To a solution of N-methyl-2-mercaptoimidazole (28 mg, 0.25 mmol) in THF (1 mL), at r.t. under N_2 atmosphere were successively added 137 (70 mg, 0.20 mmol), triphenylphosphine (70 mg, 0.27 mmol) followed by dropwise addition of diethyl azodicarboxylate (48 μ L, 0.31 mmol). The mixture was stirred for 2 h and the solvent was removed *in vacuo*. Purification by flash chromatography using MeOH/CHCl₃ (5:95) as the eluent afforded the title compound 138 (81 mg), in 91% yield, which was found to contain some diethyl hydrazodicarboxylate residus. The compound was used as is without further purification.

Step 5: N(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl]-benzamide (compound 139) [0225] Following the procedure described in Example 42, step 3, but substituting 138 for 46, the title compound 139 was obtained in 62% yield. ¹H NMR: (Acetone-d₆) δ (ppm): 9.07 (bs, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.1 Hz, 1H), 7.03-6.96 (m, 2H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.4 Hz, 1.1 Hz, 1H), 4.63 (bs, 2H), 4.29 (s, 2H), 3.42 (s, 3H).

Example 91

N-(2-Amino-phenyl)-6-(3-methoxyphenyl)-nicotinamide (compound 141)

[0226] To a mixture of 3-methoxyphenyl boronic acid (152 mg, 1.0 mmol) and 140 (248 g, 1.0 mmol) were added benzene (8 mL) and ethanol (4 mL) followed by 2 M Na₂CO₃ aqueous solution (3.2 mL, 6.4 mmol). The reaction mixture was stirred under nitrogen for 30 min and then Pd(PPh₃)₄ (58 mg, 0.05 mmol) was quickly added. After 24 h of reflux, the mixture was cooled to room temperature, filtered through a pad of celite and rinsed with ethyl acetate (30 mL). The organic solution was washed with brine (5 mL), dried (MgSO₄), and concentrated. Purification by flash silica gel chromatography (Hexane/Ethyl acetate: 1/1) afforded 141 (302 mg, 95% yield). 1 H NMR (CDCl₃) 3 8 (ppm): 9.11 (d, J = 1.8 Hz, 1H), 8.30 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.36 (m, 1H), 7.22 (m, 1H), 7.09-6.78 (m, 4H), 3.84 (s, 3H), 3.39 (br s, 2H).

a. p-aminomethylbenzoic acid/AcOH/5 min/refluxb. HOBT/EDC/1,2-diamino benzene

Example 92

N-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144) Step 1: 4(1-0xo-1,3-dihydro-isoindol-2-ylmethyl)-benzoic acid (compound 143)

[0227] To a solution of benzene-1,2-carbaldehyde 142 (1.0 g, 7.46 mmol) in 10 mL of acetic acid was added 4-aminomethylbenzoic acid (1.13 g, 7.46 mmol). The reaction mixture was refluxed 5 min and cooled to the room temperature. A crystalline precipitate was formed and triturated with CH₂Cl₂ to produce the title compound 143 (1.29 g, 49%).

Step 2: N(2-Amino-phenyl)-4(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144)

[0228] To a solution of the carboxylic acid (0.32 g, 0.89 mmol) in DMF (8 mL) at rt, was added HOBt (0.16 g, 1.15 mmol) and EDC (0.25 g, 1.33 mmol) and the solution was stirred for 1.5 h.

Lastly, phenylenediamine (0.12 g, 1.07 mmol) was added and the mixture was allowed to stir for 18-20 h. DMF was removed *in vacuo* and the crude was partitioned between ethyl acetate and H_2O . The organic layer was dried over Na_2SO_4 and concentrated. Purification by column chromatography (CH₂Cl₂-MeOH (19:1)) afforded **144** in 46% yield. ¹H NMR: (DMSO-d₆) \square 9.71 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.55-7.70 (m, 3H), 7.46 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 4.93 (bs, 2 H), 4.87 (s, 2 H), 4.47 (s, 2 H).

- a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
- b. HOBT/EDC/1,2-diamino benzene
- c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
- d. PhNTf₂/NaH/THF-DMF/30 min/0°C
- e. 1. CO/Pd(OAc)₂/dppf/Et₃N/MeOH-DMF/4 days/75°C
 - 2. AcOH/HCI/3 hrs/reflux

Example 94

N-(2-Amino-phenyl)- 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 149)

[0229] Phthalic anhydride 148 (1.3 g, 8.9 mmol) and 4-aminomethylbenzoic acid in 20 mL acetic acid were refluxing for 3 h, cooled to the room temperature and evaporated to yield a solid residue which was triturated with water, filtered off and dried to produce the intermediate carboxylic acid (1.7 g, 68%). LMRS = 282.0 (M+1).

[0230] Following a procedure analogous to that described in Example 92, step 2, but substituting the acid for **143**, the title compound **149** was obtained in 17% yield. 1 H NMR: (DMSO d₆) 0.9.59 (s, 1H), 0.7.82-0.91 (m, 6H), 0.7.40 (d, 0.9.91 = 8.0 Hz, 2H), 0.9.91 (d, 0.9.91 = 8.0 Hz, 1H), 0.9.91 (d, 0.9.91 = 8.0 Hz, 1H), 0.9.91 (t, 0.9.91 = 9.0 Hz, 1H), 0.9.91 (t, 0.9.91 (t, 0.9.91 = 9.0 Hz, 1H), 0.9.91 (t, 0.9.91 (t, 0.9.91 = 9.0 Hz, 1H), 0.9.91 (t, 0.9.91 (t, 0.9.91 = 9.0 Hz, 1H), 0.9.91 (t, 0.9.91 (t, 0.9.91 + 9.0 Hz, 1H), 0.9.91 (t, 0.9

Example 95

N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

Step 1: 2-[2-(4-Hydroxy-phenyl)-ethyl]-isoindole-1,3-dione (compound 150)

[0231] Following a procedure analogous to that described in Example 94, step 1, but substituting 4-aminomethylbenzoic acid for tyramine the title compound 150 was obtained in 48% yield. LMRS = 268.0 (M+1).

Step 2: 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl)-phenyl trifluoromethane-sulfonate (151)

[0232] To a solution of sodium hydride (90 mg, 25 mmol) in dry THF (20 mL) at 0°C, **150** (500 mg, 8.9 mmol) was added followed by the addition of dry DMF (2 mL). The reaction mixture was stirred for 20 min at 0°C, treated portionwise with PhN(Tf)₂, stirred for additional 2 h and evaporated to produce a solid material which was purified by chromatography on a silica gel column, (CH₂Cl₂ – MeOH (19:1)) to provide **151** (639 mg, 86% yield). LMRS = 400.0 (M+1).

Step 3: N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

[0233] Following a procedure analogous to that described in Example 40, step 2, but substituting **151** for **42**, the title compound **152** was obtained in 15% yield. 1 H NMR: (DMSO d₆) $^{\circ}$ I 9.57 (s, 1H), 7.78-7.87 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 6.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.83 (bs, 2 H), 3.85 (t, J = 7.1 Hz, 2 H), 3.00 (t, J = 7.1 Hz, 2 H).

Example 96

N-(2-Amino-phenyl)-4-(4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 154)

[0234] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et_3N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride **153** (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and evaporated to form an oily residue, which was refluxing in formic acid (20 mL) for 7 h. Formic acid was removed in vacuum to produce a solid, which was triturated with water and filtered off to provide the carboxylic acid (1.61 g, 96%). LMRS = 281.0 (M+1).

[0235] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 154 was obtained was obtained in 43% yield. 1 H NMR: (DMSO d₆) $^{\circ}$ D 9.71 (s, 1H), 8.68 (s, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.4, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.35 (s, 2 H).

Example 97

N-(2-Amino-phenyl)-4-(4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide (compound 155)

[0236] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et₃N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40° C and cooled to 0° C. The cold reaction mixture was acidified with conc. HCl (5 mL) and treated drop wise with NaNO₂ solution (520 mg, 7.5 mmol in 5 mL water) over 5 min period of time, then left overnight at room temperature. A precipitate formed which was collected, washed with water and dried to provide the carboxylic acid (1.62 g, 96%). LMRS = 282.0 (M+1).

[0237] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 155 was obtained in 27% yield. 1 H NMR: (DMSO d₆) \square 9.62 (s, 1H), 8.25 (t, J = 6.7 Hz, 2H), 8.11 (ddd, J = 7.1 Hz, 1.4 Hz, 1H), 7.93-7.98 (m, 3H), 7.49 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.66 (s, 2 H), 4.87 (bs, 2 H).

Example 98

N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 157)

Step 1: 4-[(2-Amino-benzoylamino)-methyl]-benzoic acid (compound 156)

[0238] To a suspension of 4-aminomethylbenzoic acid (5.09 g, 33.7 mmol) in H_2O (50 mL), was added Et_3N (4.7 mL, 33.7 mmol) followed by isatoic anhydride 153 (5.0 g, 30.6 mmol). The brown mixture was heated at 40°C for 2 h until the mixture became homogeneous and then Et_3N was removed in vacuo. The resulting aqueous solution was acidified (10% HCl/H_2O) and the mixture was partitioned between H_2O and ethyl acetate. The combined organic extracts were dried over Na_2SO_4 , filtered and evaporated to give 156 as a white solid (6.0 g, 72 %). LMRS = 271.0 (M+1).

Step 2: N42-Amino-phenyl)-4-{2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 157)

[0239] The carboxylic acid 156 (1.72 g, 6.36 mmol) was suspended in a solution of NaOH (2.55 g, 63.6 mmol) in H_2O (12 mL). To this solution was added dioxane (10 mL) until mixture became homogeneous. The solution was cooled to 0°C in an ice-bath and methyl chloroformate (1.25 mL, 16.1 mmol) was added portionwise over 2 h. After completion of the reaction, the excess methyl chloroformate and dioxane were removed *in vacuo* and the mixture was diluted with methanol (80 mL) and H_2O (20 mL). The solution was heated to 50°C for 1 h. until the cyclization was complete. Methanol was removed in vacuo and then the aqueous layer was extracted with ethyl acetate. Subsequently, the aqueous phase was acidified (10% HCI/H_2O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were combined, dried over Na_2SO_4 , filtered and evaporated to dryness. The resulting crude was triturated with warm methanol to afford the carboxylic acid as a white solid (1.7 g, 90%). LMRS = 319.0 (M+Na).

[0240] Following a procedure analogous to that described in Example 92, step 2, but substituting the quinazolinedione carboxylic acid for **143**, the title compound **157** was obtained. 1 H NMR: (DMSO-d₆) $^{\circ}$ $^{\circ}$ $^{\circ}$ 11.56 (brs, 1H), 9.59 (brs, 1H), 7.96-7.88 (m, 3H), 7.67 (dt, J = 8.4, 1.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.57 (t, J = 6.9 Hz, 1H), 5.15 (brs, 2H), 4.86 (brs, 2H).

Example 99

N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)

Step 2: 4(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid methyl ester [0241] To a solution of the quinazolinedione carboxylic acid (1.0 g, 3.38 mmol) in DMF (7 mL), was added K₂CO₃ (1.4 g, 10.1 mmol) and the mixture was then cooled to 0°C. Subsequently, Mel (1.05 mL, 16.9 mmol) was added and the mixture was allowed to warm to rt in the ice bath overnight. Excess methyl iodide and DMF were removed *in vacuo* and the crude was partitioned between ethyl acetate and H₂O. The aqueous phase was washed again with ethyl acetate, the

combined organic extracts were dried over Na₂SO₄ and then concentrated in vacuo to yield the

desired product as an off-white solid (0.93 g, 85%). LMRS = 325.0 (M+1). Step 3: 4(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid

[0242] To a suspension of the methyl ester (1.25 g, 3.85 mmol) in methanol (35 mL), was added 1N NaOH (30 mL, 38.5 mmol) and the mixture was heated to 45-50°C for 3 h. until it became homogeneous. Methanol was removed *in vacuo* and the crude was partitioned between ethyl acetate and H_2O . The aqueous phase was acidified (10% HCl/H2O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford product 5 as a white solid (1.15 g, 96%). LMRS = 311.0 (M+1).

Step 4: N(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound **158**)

[0243] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 158 was obtained in 10% yield. 1 H NMR: (DMSO-d₆) δ 9.59 (brs, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H) 7.80 (dt, J = 6.9, 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.21 (brs, 2H), 4.86 (brs, 2H), 3.54 (s, 3H).

Example 100

N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 159)

[0244] A suspension of 156 (903 mg, 3.34 mmol) in acetic anhydride (15 mL) was heated at 50°C for 1 h. Acetic anhydride was evaporated under vacuum and the solid material formed was

dissolved in acetic acid (30 mL). This solution was refluxed 48h and evaporated to form another solid material, which was recrystallized from a mixture AcOEt/CHCl₃ to produce the intermediate carboxylic acid (420 mg, 43% yield). LMRS = 385.0 (M+1).

[0245] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 159 was obtained in 49 % yield. 1 H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H, overlaps with the DMSO signals).

Example 101

N-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound 163) Step 1: 4-Methoxybenzyl-thiourea (compound 161)

[0246] To a solution of thiocarbonyl diimidazole (1.23g, 6.22 mmol, 1.5 equiv.) in dry dichloromethane (10 mL), neat alkylamine 160 (4.15 mmol, 1.0 equiv.) was added dropwise at 0°C, and the solution stirred from 0°C to 15°C during 16 h. A solution of concentrated ammonium hydroxide (3 mL, 45 mmol, 3.6 equiv.) in 1,4-dioxane (6 mL) was added at 0°C and stirred at room temperature for 7 h. The solution was diluted with ethyl acetate (250 mL), washed with brine (2 x 50 mL), dried (MgSO₄), filtered and concentrated. After purification by column chromatography (silica gel, elution 5% methanol in dichloromethane), 161 was obtained as yellow solid (700.2 mg, 3.6 mmol, 86% yield). 1 H NMR: (Acetone-d₆) δ (ppm): 7.53 (bs, 1H), 7.28 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.67 (bs, 2H), 4.67 (s, 2H), 3.77 (s, 3H). LMRS = 197.1 (M+1).

Step 2: 2-(4-Methoxybenzylamino)thiazole-5-carboxylic acid methyl ester (compound 162)

[0247] A solution of trans methyl-2-methoxyacrylate (461 mg, 3.97 mmol, 1 equiv.) in 50% 1,4-dioxane in water (4 mL) stirred at -10° C, was treated with N-bromosuccinimide (792 mg, 4.46 mmol, 1.12 equiv.), stirred at the same temperature for 1h, transferred to a flask containing the thiourea 161 (700.2 mg, 3.6 mmol) and the mixture was stirred at 80°C for 2h. After cooling down to room temperature, concentrated NH₄OH (0.8 mL) was added, stirred for 10 min and the resulting precipitated filtered and washed with water, giving 363 mg (1.3 mmol, 36% yield) of 162, plus 454 mg additional (91 % pure by HPLC) as residue from evaporation of the filtrated (ca. 77% overall yield). ¹H NMR: (Acetone-d₆) δ (ppm): 7.97 (bs, 1H), 7.72 (bs, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H). LMRS = 279.1 (M+1).

Step 3: N(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound 163)

[0248] Following the procedure described in Example 1, steps 4 and 5, but substituting 162 for 6, the title compound 163 was obtained in 50% yield. 1 H-NMR (methanol-d4), δ (ppm): 7.86 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.04 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.86 (m, 1H), 6.74 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.85 (bs, 4H), 4.45 (s, 2H), 3.78 (s, 3H).

Examples 102-121

[0249] Examples 102 to 121 describe the preparation of compounds **164** to **183** using the same procedures as described for compounds **62** to **163** in Examples 47 to 101. Characterization data are presented in Tables 4a and 4b.

Table 4a

Characterization of Compounds Prepared in Examples 102-121

¥	•
IZ >=0	

EX.	Pd S	M	>	2	Name	Characterization	Schm
102	164	MeO	공	동	CH M2-Amino-phenyl)-4-	s, 1H), 7.99 (d, J =	11
		> >			[(3,4,5-trimethoxy-	8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.7 Hz,	
		Мео			phenylamino}-methyl]-	1H), 7.00 (t, J = 6.6 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.1 Hz,	
		OMe			benzamide	1H), 6.67 (t, J= 8.0 Hz, 1H), 5.99 (s, 2H), 5.46 (bs, 1H), 4.64	
						(bs, 2H), 4.43 (s, 2H), 3.69 (s, 6H), 3.60 (s, 3H).	
103	165		z	ᆼ	CH M2-Amino-phenyl)-6-(3-	¹ H NMR (20% CD ₃ OD in CDCl ₃) 8 (ppm): 9.14 (d, J = 1.8	15
- /		<u></u>			hydoxymethyl-phenyl)-	Hz, 1H), 8.33(dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.93 (s, 1H), 7.82	
		_₹			nicotinamide	(m, 2H), 7.50-7.40 (m, 2H), 7.22-6.45 (m, 4H), 4.69 (s, 2H).	···
104	166		동	동	CH M2-Amino-phenyl)-4-(3-	¹ H NMR (CD ₃ OD) 8 (ppm): 7.98 (d, J = 8.4 Hz, 2H), 7.65 (d, J	15
		<u> </u>			methoxy-phenyl}-	= 8.4 Hz, 2H), 7.31-7.04 (m, 5H), 6.92-6.80 (m, 3H), 3.84 (s,	
		ОМе			benzamide	3H).	
105	167	HN /	H	z	N M2-amino-phenyl)-6-(4-	¹ H NMR (DMSO-d ₆) δ (ppm): 9.33 (s, 1H), 8.61 (d, J = 2.5	9
		MeO			methoxy-benzylamino}-	Hz, 1H), 7.89 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 5.8 Hz,	
					nicotinamide	1H), 7.24 (d, J = 8.52 Hz, 2 H), 7.11 (d, J = 7.69 Hz, 1H),	
						6.90 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.50-6.58 (m, 2H),	
						4.83 (s, 2H), 4.45 (d, J = 5.8 Hz, 2H), 3.70 (s, 3H).	
106	168	¥	공	z	M(2-amino-phenyl)-6-[2-(4-	N [W(2-amino-phenyl)-6-[2-(4 14 NMR (DMSO-d ₆) 8 (ppm): 9.42 (s, 1H), 8.72 (d, J = 2.5	9
		- Ca-M			methoxy-phenyl}-	Hz, 1H), 7.97 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 7.23 (m, 4H), 6.81-	
					ethylamino}-nicotinamide	7.03 (m, 4H), 6.64 (m, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.92 (s.	
_						2H), 3.78 (s, 3H), 3.55 (m, 2H). 2.85 (t. J = 7.3 Hz. 2H).	

Schm	7.95 (d, J = 7.9 11 lz, 2H), 7.20 (d,	1H), 6.81 (d, J = , 4.94 (bs, 2H),	1H), 6.81 (d, J = , 4.94 (bs, 2H), 8.21 (d, J = 8.8 11 Hz, 1.3 Hz, 1H), 7.44 (d, J = 1, J = 7.9 Hz, t, J = 7.7 Hz,			(4) (4) (4) (4) (4) (4) (4) (4) (4) (4)
3 (bs, 1H), 7.95 (d, J:	Hz, 2H), 7.85-7.82 (m, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.03 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.9 Hz, 7.7 Hz, 1H), 4.94 (bs, 2H), 4.64 (d. J = 6.0 Hz, 2H), 2.20 (hz, 6H)		H. J. H. M. MR. (DMSO-ds) & (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).	⁴ .34 (u, y = 0.0 Hz, 2H), 3.73 (u3, 0H). ⁴ .4 NMR: (DMSO-d ₆) 8 (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.007.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H) 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H). ¹ H NMR: (DMSO-d ₆) 8 (ppm): 9.06 (bs, 1H), 8.17 (dt, J = 10.9 Hz, 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.01 (dt, J = 7.9 Hz, 1H), 6.62 (t, J = 8.5 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 5.01 (bs, 2H), 4.47 (s, 2H), 3.76 (s, 3H).	H. J. H. N. MR.: (DMSO-ds) & (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.007.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.79 (dd, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 1H), 4.69 (s, 2H). 1.4 Hz, 1H), 4.69 (s, 2H). 1.4 Hz, 1H), 4.69 (s, 2H). 1.5 Hz, 1H), 8.17 (dt, J = 8.5 Hz, 1H), 8.17 (dt, J = 10.9 Hz, 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.21-7.13 (m, 2H), 7.01 (dt, J = 7.9 Hz, 1H), 6.62 (t, J = 8.5 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 8.2 Hz, 2H), 7.90 (dd, J = 4.4 Hz, 0.6 Hz, 1H), 7.37 (dd, J = 8.2 Hz, 2H), 7.90 (dd, J = 4.4 Hz, 0.6 Hz, 1H), 7.37 (dd, J = 7.1 Hz, 1.1 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.58 (t, J = 6.6 Hz, 1H), 4.88 (s, 2H), 4.73 (s, 2H).	#34 (u, J = 8.0 ftg, J21), 3.73 (B3, 1H), 8.21 (d, J = 8.8 (quinolin-2-4 ftg), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 8.00-7.89 (m, 4H), 7.75 (dd, J = 6.8 Hz, 1.1), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.90 (dz, J = 7.9 Hz, 1H), 7.21-7.13 (m, 2H), 7.01 (dt, J = 7.9 Hz, 1H), 6.62 (dz, J = 8.5 Hz, 1H), 7.29 (dz, J = 8.5 Hz, 1H), 7.39 (dz, J = 8.2 Hz, 1H), 7.63 (dz, J = 8.0 Hz, 1H), 7.63 (dz, J = 8.0 Hz, 1H), 7.63 (dz, J = 8.2 Hz, 1H), 7.39 (dz, J = 8.0 Hz, 1H), 7.37 (dz, J = 8.2 Hz, 2H), 7.14 (dz, J = 8.0 Hz, 1H), 7.37 (dz, J = 8.2 Hz, 1H), 6.76 (dz, J = 8.0 Hz, 1H), 6.66 (dz, J = 6.4 Hz, 1H), 6.66 (dz, J = 8.2 Hz, 1H), 6.72 (dz, J = 8.0 Hz, 1H), 7.37 (dz, J = 8.2 Hz, 1H), 6.74 (dz, J = 7.7 Hz, 1H), 6.75 (dz, J = 7.7 Hz, 1H), 6.76 (dz, J = 7.7 Hz, 1
CH M{2-Amino-phenyl}-4-[{4,6- 14 NMR: (DMSO-d ₆) 8 (ppm): 9.63 (bs, 1H), 7.95 (d, J = 7.9 dimethoxy-pyrimidin-2- Hz, 2H), 7.85-7.82 (m, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.20 (d,	t, J = 7.6 Hz, 7.4 H = 7.9 Hz, 7.7 Hz, 1, , 3.79 (bs, 6H).	(nnm): 9 62 (he 1H	(H), 7.79 (dd, J = 6. H), 7.79 (dd, J = 6.8 Hz 7.56 (t, J = 6.8 Hz = 8.2 Hz, 1H), 6.99 = 6.9 Hz, 1H), 6.61	(H), 7.79 (dd, J = 6.8 Hz, 7.56 (t, J = 6.8 Hz, 1.14), 6.99 = 6.9 Hz, 1.14), 6.61 J. (ppm): 9.06 (bs, 11-46 (d, J = 8.5 Hz, 1.14), 7.01 (dt, J = 7.24), 6.80 (d, J = 7.24), 4.47 (s, 2.24), 4.47 (s, 2.24)	(hp) (h) (h) (h) (h) (h) (h) (h) (h) (h) (h	(hp) (h) 7.79 (dd, J = 6.8 Hz, 7.56 (t, J = 6.8 Hz, 1.14), 6.99 (e.9 Hz, 1.14), 6.61 (h) 8.00 (bs, 1.14), 6.81 (h) 9.00 (bs, 1.14), 6.80 (d, J = 7.2 Hz, 0.8 H
MSO-d ₆) δ (ppm) -7.82 (m, 1H), 7 H), 7.03 (dt, J =	7.3 nz, 1ni, 0.03 (dt, J = 7.3 nz, 7.7 n 4.54 (d, J = 6.0 Hz, 2H), 3.79 (bs, 6H).	WSO-d ₆) 8 (ppm -7.89 (m, 4H), 7	5.3 Hz, 2H), 7.56 7.17 (d, J = 8.2 6.79 (d, J = 6.9 4.69 (s, 2H).	5.3 Hz, 2H), 7.56 7.17 (d, J = 8.2 6.79 (d, J = 6.9 4.69 (s, 2H). MSO-ds) 8 (ppm Hz, 1H), 7.46 (c 7.21-7.13 (m, 2l J = 8.5 Hz, 2H) J = 8.5 Hz, 2H)	5.3 Hz, 2H), 7.56 7.17 (d, J = 8.2 6.79 (d, J = 6.9 6.79 (d, J = 6.9 4.69 (s, 2H). MSO-de) & (ppm, 2H, 1H), 7.46 (d 7.21-7.13 (m, 2H, 2H), 7.21-7.13 (m, 2H, 2H), 7.20 (dd, 2H), 7.90 (dd, 2H), 7.48 (dt, J = 1H), 7.14 (dd, J = 7.7 4.73 (s, 2H).	5.3 Hz, 2H), 7.56 7.17 (d, J = 8.2 6.79 (d, J = 6.9 4.69 (s, 2H). 4.69 (s, 2H). 4.60 (s, 2H). 7.21-7.13 (m, 2l) J = 8.5 Hz, 2H), 7.21-7.13 (m, 2l) 7.21-7.13 (m, 2l) 7.21-7.13 (m, 2l) 7.21-7.14 (dd, 2l) 7.14 (dd, J = 7.7 4.73 (s, 2H). 4.73 (s, 2H). 6.76 (d, J = 7.7 4.73 (s, 2H). 6.76 (d, J = 7.7 4.73 (s, 2H). 6.76 (d, J = 9 Hz, 3l), 6.90-6.96
¹ H NMR: (DM Hz, 2H), 7.85- J = 7.1 Hz, 1H	7.9 Hz, 1H), 6 4.54 (d, J = 6	¹ H NMR: (DM Hz, 1H), 8.00- 7.68 (d, J = 6 8.7 Hz, 1H), 7	7.4 Hz, 1H), 6 7.4 Hz, 1H), 4	7.4 Hz, 1H), 6.79 (d, J = (7.4 Hz, 1H), 6.79 (d, J = (7.4 Hz, 1H), 4.69 (s, 2H). 1.4 NMR: (DMSO-d ₆) δ (p. 10.9 Hz, 9.0 Hz, 1H), 7.44 8.2 Hz, 2H), 7.21-7.13 (m. 1H), 6.91 (d, J = 8.5 Hz, (t, J = 7.4 Hz, 1H), 5.01 (f)	7.4 Hz, 1H), 6 7.4 Hz, 1H), 4 1.4 Hz, 1H), 4 10.9 Hz, 9.0 Hz, 9.0 Hz, 1H), 6.91 (d, 1H), 6.91 (d, 1Hz, 1Hz, 1Hz, 1Hz, 1Hz, 1Hz, 1Hz, 1Hz	7.4 Hz, 111, 6.79 (d, J = 6 7.4 Hz, 111, 6.79 (d, J = 6 7.4 Hz, 111, 6.79 (d, J = 6 10.9 Hz, 9.0 Hz, 111, 7.46 8.2 Hz, 211, 7.21-7.13 (m, 111), 6.91 (d, J = 8.5 Hz, 2 (t, J = 7.4 Hz, 111), 5.01 (b) 14. NMR: (DMSO-ds) 8 (pp (d, J = 8.2 Hz, 211), 7.90 (d, J = 8.2 Hz, 211), 7.48 (dt, 3 = 7.1 Hz, 1.1 Hz, 111), 7.1 6.3 Hz, 111, 6.76 (d, J = 7 4.88 (s, 211), 4.73 (s, 211). 14. NMR (DMSO-ds) 8 (pp Hz, 111), 7.89 (dd, J = 9 Hz) 7.06-7.20 (m, 311), 6.90-6.
10-phenyl)-4-[(4,6-	dimethoxy-pyrimidin-2- ylamino}-methyl]- benzamide	/K/2-Amino-phenyl)-4- (quinolin-2- ylsulfanylmethyl)- benzamide		N-(2-Amino-phenyl)-6-(4- methoxy-benzylsulfanyl)- nicotinamide		(4- 1y1)- 12-(4- nino)-
I M2-Amin	dimethoxy-pyrim ylamino)-methyll- benzamide	M.CAmino-pheny (quinolin-2- ylsulfanylmethyl)- benzamide			M(2-Amino-pheny methoxy-benzylsı nicotinamide nicotinamide N(2-Amino-pheny (benzothiazol-2- ylsulfanylmethyl)- benzamide	M(2-Amino-pl methoxy-ben nicotinamide i M(2-Amino-p (benzothiazo ylsulfanylmet benzamide benzamide M(2-amino-pl fluoro-phenyl nicotinamide
공 공		동 동		J N		
`	~~	<u></u> ω_/		<u></u>	\(\sigma_{\nu}\)),
•	MeO NO	Z		Мео	Me So	No.
	169	170		171	171	171 172 172
	107	108		60	10	110

Cpd W Y Z Name	Y Z	2	Nan	ne	Characterization	Schm
2	2	2	13	04	Vial acter (Calloi)	SCHIT
We o	5	z	/\{2-amir (3,4,5-tri	/k{ <i>2</i> -amino-phenyl}-6- (3,4,5-trimethoxy-	'H NMR (DMSO-d ₆) δ (ppm): 9.34 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 6 Hz,	9
ОМе		benzylamin	benzylamin	o)-nicotinamide	benzylamino)-nicotinamide 1H), 7.10 (m, 1H), 6.93 (m, 1H), 6.74 (m, 1H), 6.66 (s, 2H), 6.56 (m, 2H), 4.84 (s, 2H), 4.45 (d, J = 6 Hz, 2H), 3.73 (s, 6H), 3.31 (s, 3H)	
177 N-N-S CH CH N42-Amino	공	공	M2-Amino	N42-Amino-phenyl)-445-	14 NMR: (Acetone-de) δ (ppm); 9.08 (bs. 1H). 8.02 (dd. J ≡	14
phenyl-[1,3,4]ox:	phenyl-[1,3	phenyl-[1,3 ylsulfanylm	phenyl-[1,3	phenyl-[1,3,4]oxadiazol-2- ylsulfanylmethyl]-	7.1 Hz, 1.9 Hz, 4H), 7.69 (d, J = 8.5 Hz, 2H), 7.62-7.57 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, 1 = 7.7 Hz, 1H), 6.86 (d, 1 =	
			benzamide		6.6 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 4.70 (s, 2H), 4.63 (bs, 2H).	
1/8 N CH M2-aminophenyl)-6-(2-phenylamino-ethylamino	ᆼ	ᆼ	N(2-amino phenylamir	승	¹ HNMR (CD ₃ OD-44), δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J= 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15	11
nicotinamide	nicotinamic	nicotinamic	nicotinami		(dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0	
					Hz, 1.4 Hz, 1H), 6.76 (dt, J= 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t. J = 6.3 Hz,	
	T	T		\neg	2H), 3.35 (t, J = 6.3 Hz, 2H).	
1/9 CH CH M2-Amino-			N(2-Amino-	N(2-Amino-phenyl)-4-(2,4-	¹ H NMR: (DMSO-d ₆) δ (ppm): 9.62 (s, 1H), 8.00 (dd, J = 8.2	11
N N N N N N N N N N N N N N N N N N N	NN / GIOXO4H	dloxo-4H-	dloxo-4H-		Hz, 1.9 Hz, 1H), 7.80-7.92 (m, 3H), 7.42-7.50 (m, 4H), 7.13	
Vimethyll-benzamide) Serizoleiti;		venzolent		(d, J = 7.1 hZ, 1H), 6.95 (ddd, J = 8.0 HZ, 1.6 HZ, 1H), 6.75 (dd) = 8 0 Hz, 1 4 Hz, 1 H), 6.55 (dd) = 8 0 Hz, 1 L), 6.15 (c)	
					2H), 4.87 (bs, 2H).	
180 CH CH M2-Amino	공	공			¹ H NMR: (DMSO-d ₆) & (ppm): 9.59 (s, 1H), 7.88 (d, J = 8.2	Ξ
Me ethyl-4-met	ethyl-4-met	ethyl-4-met	ethyl-4-met	- oxo	Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H),	
Me benzamide	benzamide	benzamide	benzamide		0.33 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 1 7.4 Hz. 1H), 4.87 (s, 2H), 4.86 (hs, 2H), 2.61 (s, 2H), 2.55 (s, 1	
					2H), 1.31 (q, J = 7.7 Hz, 2H), 0.91 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H).	
181 CH CH (M2-Amino-phenyl)-4-(1-			M2-Amino- ethyl-2,4-di		¹ H NMR: (CDCl ₃) δ (ppm): 8.23 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 8.01 (bs. 1H) 7.80 (d. l = 8.0 Hz, 2H) 7.71.7 65 (m. 1H)	19
		dihydro-2H	dihydro-2H	dihydro-2H-quinazolin-3-	7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (dt, J = 7.7,	
et [ylmethyl)-benzamide		ylmethy()-b	ylmethyl)-b		5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3	
					Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H).	

	N	>	7	Name	Characterization	Schm
); z }=	Ş	끙	동	N(2-Amino-phenyl)-4-(4,6-	CH N42-Amino-phenyl)-4(4,6- 14 NMR: (DMSO-de) 8 (ppm): 9.66 (bs, 1H), 7.96 (d, J = 7.9	11
-z -				dimethyl-pyrimidin-2-	Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H),	<u>-</u>
 -				ylsulfanylmethyl)	7.04-6.99 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (t, J = 7.4	
				benzamide	Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).	•
я- я-		끙	끙	CH M2-Amino-phenyl)-4-(4-	¹ H NMR: (DMSO-d ₆) 8 (ppm): 9.66 (bs, 1H), 9.07 (d, J = 5.2	11
/ /-	$\left\langle \right\rangle$			trifluoromethyl-pyrimidin-2-	trifluoromethylpyrimidin-2- Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.78 (d, J = 4.7 Hz, 1H),	
	-			ylsulfanylmethyl)benzamid	ylsulfanylmethyl)benzamid 7.63 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.01 (dt, J	
				υ.	= 7.7 Hz, 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.64 (dt, J =	
					7.4 Hz, 7.1 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H).	

Table 4b

EX.	PdS	M	_	Z	Z Name	Characterization	Schm
					inophenyl)-		
					4-[3-(pyridin-	¹ H NMR (20% CD ₃ 0D in CDCl ₃) 8 (ppm): 8.46 (m,	
123	187	, , , , , , , , , , , , , , , , , , ,	끙	뚱	CH CH 2ylmethyl-	1H), 7.95 (d, J = 8.4 Hz, 2H), 7.64-6.70 (m, 14 H),	21
					aminomethyl)phen 3.80 (br s, 4H).	3.80 (br s, 4H).	
					yl)]-benzamide		
		X			Biphenyl-4,4'-	¹ H NMR (CD ₃ OD) 8 (ppm): 9.80 (bs, 2H), 8.16 (d,	
124	100	, =\ 12 + -	2	7	dicarboxylic acid	J=7.9 Hz, 4H), 7.96 (d, J= 7.9 Hz, 4H), 7.23 (d, J=7.4	
+21	001) 	5		bis-[(2-amino-	Hz, 2H), 7.03 (dd, J=6.9, 7.4 Hz, 2H), 6.84 (d, J=8.2	-
) }			phenyl}-amide]	Hz, 2H), 6.66 (dd, J=6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).	
		,			N42-Amino-phenyl)-	M(2-Amino-phenyl) 14 NMR (DMSO-4-18 (npm): 10 15 (1H brs) 8 17	
		¥_=			4-[4-{(3,4,5-	1 1 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2	
1		MeO	:	;	trimethoxv-	(211, u, J=0.V), 1.30 (211, u, J=0.2/, 1.6) (111, u)s/,	
125	189))	£	CH CH	nhonviernin	7.72 (1H, d, J=6.6), 7.54 (2H, m), 7.40 (1H, d, J=8.5), [21	[2]
		MeO				7.25 (1H, m), 7.16 (1H, d, J=7.4), 7.07 (1H, m), 6.08	
		ÓMe			-11/11/	(2H. s), 4.42 (2H. s), 3.73 (6H. s), 3.58 (3H. d. J=0.8)	
			_		penzamide		

EX.	pd C	M	\	Z	Name	Characterization	Schm
126	190	MeO H	픙	끙	N-(2-Amino-phenyl)-4-[4-(14-methoxy-phenylamino)-methyl}-phenyl]-benzamide	N42-Amino-phenyl)- 14 NMR (DMSO-ds) 8 (ppm): 10.03 (1H, brs), 8.17 4-{4-{(4-methoxy-(2H, d, J=7.7), 7.88 (3H, m), 7.76 (1H, d, J=7.1), 7.52 phenylamino}- (2H, m), 7.35 (1H, d, J=8.0), 7. 17 (1H, m), 7.08-6.93 methyl}-phenyl}- (6H, m), 4.50 (3H, s), 3.75 (2H, s)	21
128	193	H ₂ C / CH ₃	용	끙	phenyl)- but-3-	LRMS calc: 276.03, found: 277.2 (MH)*	22
129	194	- Ho	끙	끙	M.C.Amino-phenyl)- 4-(1-hydroxy- cyclohexylethynyl)- benzamide	M2-Amino-phenyl)- 441-hydroxy- cyclohexylethynyl)- LRMS calc: 334.4, found: 335 (MH)* benzamide	22
130	195	H ₃ C OH	H _O	ъ С	N42-Amino-phenyl)- 4-(3-hydroxy-3- methyl-but-1-ynyl)- benzamide	LRMS calc: 294.35, found: 295.1 (MH)*	22
131	196	_=\{	당	끙	M{2-Amino-phenyl}- 4-phenylethynyl- benzamide	LRMS calc: 312.37, found: 313.2 (MH)*	22
180	320	CI	Н	СН	N(2-Amino-phenyl)-4-[(5-chloro-benzooxazol-2-ylamino)-methyl]-benzamide	14 NMR: (Acetone-d ₆) & (ppm): 9.67 (s, 1H), 8.85 (s, 14.2-4mino-phenyl) 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 5.22 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.3 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), benzamide 6.65 (t, 7.0 Hz, 1H), 4.94 (s, 2H), 4.67 (d, J = 5.3 Hz, 2H).	35

Ex.	Cpd	M	<u>></u>	7	Z Name	Characterization	Schm
181	321	CI NHN-NH	CH CH		N{2-Amino-phenyl}-4-{[4-{4-chloro-phenyl}-phenyl}-thiazol-2-ylamino]-methyl}-benzamide	¹ H NMR: (DMSO-d ₆) 8 (ppm): 9.67 (bs, 1H), 8.36 (t, J = 5.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.02 (t, J = 8.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 7.1 Hz, 1H), 4.92 (bs, 2H), 4.65 (d, J = 5.8 Hz, 2H).	35
182	322	Br NH	СН	СН	N{2-Amino-phenyl}-4-[(5-bromo-benzothiazol-2-ylamino)-methyl]-benzamide	¹ H NMR: (DMSO-d ₆) δ (ppm): 6.97 (s, 1H), 8.78 (bs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 8.00 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 4.94 (s, 2H), 7.74 (d, J=5.9 Hz, 2H).	33, 34
183	323	MeO OMe	СН		N4(2-Amino-phenyl)- 4-{5-[(3,4,5- trimethoxy- phenylamino)- methyl]-thiophen-2- ylmethyl}- benzamide	LRMS calc: 489.58, found: 490 (MH)*	21
184	325	S S H	СН		N42-Amino-phenyl)- 4-{6-[(pyridin-3- ylmethyl)-amino]- benzothiazol-2- ylsulfanylmethyl}- benzamide	At C-Amino-phenyl) 14 NMR: (Acetone-d ₆) & (ppm): 8.65 (d, J = 1.4 Hz, 4-{6-[(pyridin-3-1H), 8.44 (dd, J = 4.7, 3.0 Hz, 1H), 7.97 (d, J = 8.2 ylmethyl)-aminol Hz, 2H), 7.81-7.77 (m, 1H), 7.63 (m, 3H), 7.33-7.26 (m, 2H), 7.09 (d, J=2.5 Hz, 1H), 7.02-6.97 (m, 1H), sysulfanylmethyll- 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.86 (dd, J = 8.0, 1.4 benzamide Hz, 1H), 6.69-6.64 (m, 1H), 4.64 (s, 2H), 4.47 (s, 2H).	11

	W	<u>'</u>	N Z	Name	Characterization	Schm
ZI	S	Э НЭ	CH V V V V	14. W(2-Amino-phenyl)- (m. 4-(6-[(pyridin-2- Hz ylmethyl)-amino]- 7.2 benzothiazol-2- (m. ylsulfanylmethyl)- 2.5 benzamide 114	¹ H NMR: (DMSO-d ₆) 8 (ppm): 9.59 (s, 1H), 8.52-8.51 (m, 1H), 7.89 (d, J= 8.24 Hz, 2H), 7.71 (td, J = 7.7,1.9 Hz, 1H), 7.59-7.53 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.12 (d, J = 6.9, Hz, 1H), 6.98-6.96 11, 9henzothiazol-2. (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.81 (dd, J = 9.1, 38 ulfanytmethyl) (m, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.87 (s, 1H), 4.58 (s, 2H), 4.38 (d, J = 6.3 Hz, 2H).	34
Z^ZI	-\$_{-}	СН		N(2-Amino-phenyl)- 1H) 4-(1H-imidazol-2- 7.1 ylsulfanylmethyl)- Hz, benzamide 2Hz,	NMR: (DMSO-d ₆) & (ppm): 12.23 (bs, 1H), 9.59 (s, 7.86 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 47.12 (m, 2H), 6.94-6.92 (m, 2H), 6.76 (d, J = 6.6 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H), 6.57 (t, D = 7.4 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H), 4.29 (s)	14
<u>\</u>	^λ χ ['] √ V	당	H S 4 Y d	N(2-Amino-phenyl)- 7.5 4-morpholin-4- (t, ylmethyl- = 7 benzamide = 2.5	¹ H NMR: (CD ₃ OD) & (ppm): 8.03 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 7.16 (t, J = 6.6 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 3.78 (t, J = 4.4 Hz, 4H), 3.68 (s, 2H), 2.57-2.54 (m, 4H).	37
MeO MeO	بہر کے ا	СН		3',4',5'-Trimethoxy-1H biphenyl-4- carboxylic acid (2- (t, amino-phenyl)- 1H amide	3',4',5-Trimethoxy- 14 NMR: (CD ₃ OD) & (ppm): 8.14 (d, J = 7.9 Hz, 2H), biphenyl-4- carboxylic acid (2- (t, J = 7.0 Hz, 1H), 7.04 (s, 2H), 7.00 (d, J = 8.4 Hz, amino-phenyl)- 1H), 6.87 (t, J = 7.5Hz, 1H), 4.95 (s, 6H), 4.01 (s, 3H).	37
H ₃ C	HZ Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	ਲ ਲ		4-{(2-Amino-9-butyl- = 7 9/4-purin-6-7.9 ylamino)-methyl]-N-7.3 (2-amino-phenyl)-7.3 benzamide 2H	4-{(2-Amino-9-butyl-2H), 7.95 (bs, 2H) 7.78 (s, 1H), 7.96 (d, J = 9H-purin-6-7.9 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.9 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.9 Hz, 2H), 7.3, 8.0 Hz, 1H), 6.8 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 7.3 mino-phenyl)-7.3, 7.7 Hz, 1H), 5.91 (s, 2H), 4.94 (bs, 2H), 4.77 (bs, benzamide 2H), 4.01 (t, J = 7.1 Hz, 1H), 1.78 (m, 2H), 1.3 (m, 2H), 0.95 (t, J = 7.4, Hz, 1H)	39

Schm	ک (br, π		(m, 39 (m, (m, 4, 1) = 39 d6, J	, f. f. f	, , , , , , , , , , , , , , , , , , ,
	¹ H NMR (DMSO-d ₆) δ (ppm): 10.16 (s, 1H), 9.60 (br, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.62 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.20 (m,	n, 1H), 7.20 (m,	2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H) ¹ H NIMR (DMSO-d ₆) δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7,02 (dd, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6, J = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H)	2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H) ¹ H NMR (DMSO-d ₆) δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6, J = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H) ¹ H NMR (DMSO-d ₆) δ (ppm): 9.60 (s, 1H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd, J = 6.7, 8.0 Hz, 2H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J=7.1 Hz, 3H)	2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H) ¹ H NMR (DMSO-d ₆) δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7,02 (dd, J = 6.3, R.1 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6, J = 6.3, R.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H) ¹ H NMR (DMSO-d ₆) δ (ppm): 9.60 (s, 1H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd, J = 6.7, 8.0 Hz, 2H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J=7.1 Hz, 3H) ¹ H NMR: (DMSO-d ₆) δ (ppm): 12.39 (bs, 1H), 7.21-7.17 (m, 3H), 6.99-6.97 (m, 2H), 6.81 (d, J=8.2 Hz, 1H), 6.75 (s, 1H), 4.85 (s, E7) (d, J=8.8 Hz, 2H), 6.63 (t, J=7.0 Hz, 1H), 4.85 (s, E7), 4.62 (d, J=5.3 Hz, 2H).
nm). 10 16 (c	1H), 8.24 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.62 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.20 (m, 2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H)	2H), 7.40 (m, 1 m, 2H), 4.6 (br,	¹ H NMR (DMSO-d ₆) δ (ppm): 9.67 (m, 1H), 8.8 (1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.55 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7,02 (dd, 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H)	¹ H NWR (DMSO-d ₆) δ (ppm): 9.67 (m, 1H), 8.80 (π 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7,02 (dd, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (d6 = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H) (br, 2H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd = 6.7, 8.0 Hz, 1H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J=7.1 3H)	ppm): 9.67 (m, 1 1, J = 7.8 Hz, 2P, 7.8 Hz, 1H), 7, 7.8 Hz, 1H), 7, 7.8 Hz, 1H, 7.7 (tr. 2H), 4.77 (tr. 2H), 4.77 (tr. 2H), 4.71 (m) 5.0 Hz, 1H), 6.5 (m, 2H), 0.89 (m, 2H
150-d-1 & (nn	1H), 8.08 (d,) J = 8.0 Hz, 2t, 1H), 4.90 (m,	J = 8.0 Hz, 24, 1H), 4.90 (m,	111), 7.99 (d,) 7.21 (d, J = 7. 111), 6.82 (d, J 2, 111), 4.94 (bi	111, 7.99 (d., 7.99) (d., 7.91) (d., 1.91) (d., 1.92) (d., 1.93) (d., 1.94) (b., 1.94) (b., 1.94) (b., 1.95) (d., 1.95) (1H), 8.24 (s, 1H), 7.99 (d, J. 7.8 Hz, 2H), 7.21 (d, J = 7.8 6.3, 7.8 Hz, 1H), 6.82 (d, J. 7.8 Hz, 1H), 6.82 (d, J. 7.8 Hz, 1H), 4.94 (br. 7.8 1.8 Lz, 1H), 7.92 (d, J. 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.7, 8.0 Hz, 2H), 4.88 (s, (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 1.88 (s, (m, 3H), 6.996.97 (m, 2H), 6.6.7 (d, J = 8.8 Hz, 2H), 6.6.5 (2H), 4.62 (d, J = 5.3 Hz, 2H), 4.62 (d, J = 5.3 Hz, 2H), 6.6.5 (4H), 4.62 (4H), 4.62 (4H), 4.62 (4H), 4.62 (
H NMR (DMS	H), 8.24 (s, 1 H), 7.60 (d, J H), 7.08 (m,	H), 7.60 (d, J H), 7.08 (m, H NMR (DMS	n, 6.24 (5, 1 .8 Hz, 2H), 7 .3, 7.8 Hz, 11 6.3, 8.1 Hz,	111), 8.24 (s, 17.8 Hz, 2H), 7 6.3, 7.8 Hz, 11 6.3, 8.1 Hz, 11 7.4 NIMR (DINS) 11.1, 8.21 (s, 11), 7.31 (m, 2H), 1.76 (m, 2H), 1	11, 6.24 (s, 17, 8.17, 2.3, 7.8 Hz, 2H), 7.3, 7.8 Hz, 11, 6.3, 8.1 Hz, 11, 8.21 (s, 11, 12, 13, 14, 17, 8.0 Hz, 17, 8.1 (d, 14, 17, 18, 16, 18, 18, 18, 18, 18, 18, 18, 18, 18, 18
Maille Cliai acter (Zamori	N(2-Amino-phenyl)- ¹ † 4-{(2-amino-9 <i>H</i> 1} purin-6-ylamino)- 1} methyl}-benzamide [2]	g	N(2-Amino-phenyl)- 11 4-[(2-chloro-97+ 7, purin-6-ylamino)- 6, methyl]-benzamide =	. 15 de √5 .	yl)- de yl)- de yl)-
	는 등 등			5 5	5 5 5
	ᆼ	5 5 5 5		ᆼ	
AA	HN N N N N N N N N N N N N N N N N N N		, NH N	HN CO	H N N N N N N N N N N N N N N N N N N N
pd	331	332		333	333
Ex.	190			761	192

WO 03/024448 PCT/US02/29017

Ex.	Cpd	W	_	7	Name Characterization		Schm
195	336	CI N N Me	H)		N-(2-Amino-phenyl)- 1H), 8.16 (4-(6-chloro-2- 7.95 (dd, J methyl-4-oxo-4H- 1H), 7.74 (quinazolin-3- ylmethyl)- Hz, 1H), 6.(benzamide 4.94 (bs, 2	¹ H NMR: (DMSO) 5 (ppm): 9.69 (bs, 1H, NH), 8.71 (s, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.02 (td, J = 7.6, 1.5 Hz, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.64 (td, J = 7.6, 1.4 Hz, 1H), 5.34 (s, 2H), 4.94 (bs, 2H). MS: (calc.) 404.1; (obt.) 405.0 (MH) ⁺	6
196	337	O N N We	СН	H)	¹ H NMR: (I 8.0, 1.6 Hz 8.0, 1.6 Hz 8.0, 1.6 Hz 4.2-methyl-4-oxo-1H), 7.64 (4 4H-quinazolin-3-1.1 Hz, 1H) ylmethyl)-6.77, 1.1 Hz benzamide 1.3 Hz, 1H] MS: (calc.)	H NMR: (DMSO) & (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.0 Hz, 2H), 7.95 (dd, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H).	Ø
197	338	MeO N Jr.	СН	Ю	1. NAR: (DMSO) δ N(2-Amino-phenyl)- 8.41 (d, J = 8.2 Hz, 4(6,7-dimethoxy-4- Hz, 2H), 7.17 (s, 1 H) οxo-4H-quinazolin- (ddd, J = 7.7, 7.7, 1 1H), 6.58 (dd, J = 6 benzamide (bs, 2H), 3.91 (s, 3H) (obt.) 431.1 (MH) ⁺	N-(2-Amino-phenyl)- 8.41 (d, J = 8.2 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 7.7 4-(6,7-dimethoxy-4-Hz, 2H), 7.17 (s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.96 oxo-4H-quinazolin- (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.58 (dd, J = 6.9 Hz, 1H), 5.26 (s, 2H), 4.88 benzamide (bs, 2H), 3.91 (s, 3H), 3.87 (s, 3H). MS: (calc.) 430.2; (obt.)	6
198	339		ᆼ	ᆼ	14 NMR: (1 N.(2-Amino-phenyl)- 8.07 (dd, J.) 4-(6, 7-difluoro-4- 2H), 7.82 (oxo-4H-quinazolin- 12, 2H), 7.5, 1.5 Hz benzamide (ddd, J = 7 2H), MS: (cdd, J =	¹ H NMR: (DMSO) 8 (ppm): 9.66 (bs, 1H), 8.69 (s, 1H), 8.07 (dd, J = 8.8, 10.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 14.3, 11.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1z, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.1, 1.2 Hz, 1), 6.58 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.28 (s, 2H), 4.89 (bs, 2H). MS: (calc.) 406.1; (obt.) 407.0 (MH) ⁺	6

Ę.	bd	A	<u>/</u>	2	Z Name Characterization	Schm	Ę
199	340		ъ	경	M42-Amino-phenyl) 1 H NMR: (DMSO) 1 (1 ppm): 9.61 (bs, 1H), 8.09 (dd, J. 4.114.2-1.8, 1.5 Hz, 1H), 7.91 (d, 1 = 8.2 Hz, 2H), 7.81 (ddd, 1 dimethylamino 1 7.42 (d, 1 = 8.2 Hz, 2H), 7.32 (dd, 1 = 7.6, 7.6 Hz, ethyl)-2,4-dioxo 1 1.5 Hz, 1H), 6.77 (dd, 1 = 7.8, 1.2 Hz, 1H), 6.59 (ddd, 1 = 7.6, 7.6, 1.5 Hz, 1H), 6.75 (s, 2H), 4.88 (bs, 2H), ylmethyl) 1 4.24 (t, 1 = 7.1 Hz, 2H), 2.5 (m, 2H) 2.22 (s, 6H). MS: (calc.) 457.2; (obt.) 458.1 (MH) $^{+}$, J idd, 6, 19 10,	
200	341		СН	. B	N-(2-Amino-pheny!)- "H NMR: (DMSO) & (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.81 (ddd, 4-[1-(2-morpholin-4-7.43 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 7.4, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (ddd, J = 7.4, 7.4 Hz, 1.4-dihydro-2H-1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.22 (s, 2H), 4.87 (bs, 2H), ylmethyll-4.28 (t, J = 6.7 Hz, 2H), 2.47-2.44 (m, 4H). MS: (calc.) 499.2; (obt.) 500.3 (MH)*.	fidd, 19 (6, 19 (19) (19) (58 (19) (19) (19) (19) (19) (19) (19) (19)	
201	342	Br O N N N Me	СН	H)	N.(2-Amino-phenyl)- 2.5 Hz, 1H), 7.99 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 7.95 4-(6-bromo-2- methyl-4-oxo-4H- quinazolin-3- ylmethyl)- 2.5 Hz, 1H), 7.99 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.45 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 462.1; (obt.) 463.1 (MH)*.	.95 d, J = 19	

E.	Cpd	M	<u>}</u>	7	Name	Characterization	Schm
202	343	O ZI		_	N-(2-Amino-phenyl)- 4-(2,4-dioxo-1,4- dihydro-2H- thieno[3,2- d]pyrimidin-3- ylmethyl)- benzamide	δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = '.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 'd, J = 7.1 Hz, 1H), 6.98-6.94 (m, 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, s., 2H), 4.88 (bs, 2H). MS: (calc.) 5 (MH) ⁺ .	43
203	344	0	용	ъ Б	N-(2-Amino-phenyl)- 4-(6-bromo-1-ethyl- 2,4-dioxo-1,4- dihydro-2H- quinazolin-3- ylmethyl)- benzamide	¹ H NMR: (DMSO) 8 (ppm): 9.61 (bs, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 9.1, 4.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.76 (dd, J = 8.1, 1.5 Hz, 1H), 6.78 (dd, J = 8.1, 1.5 Hz, 1H), 6.99 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.20 (s, 2H), 4.88 (bs, 2H) 4.14 (q, J = 7.0, 2H), 1.21 (t, J = 7.0, 3H). MS: (calc.) 492.1; (obt.) 493.0 (MH) ⁺ .	19
204	345	OMe OMe	ъ ъ	ъ В	N-(2-Amino-phenyl)- 4-[1-(4-methoxy- benzyl)-2, 4-dioxo- 1, 4-dihydro-2H- quinazolin-3- ylmethyl}- benzamide	N42-Amino-phenyl) 7.7, 1.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.71 (ddd, J = 4.1.44-methoxy = 7.9, 7.9, 1.5 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.38 oenzyl)-2,4-dioxo- (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 6.6 Hz, 1H), 6.96 (ddd, J = quinazolin-3- (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.50 (dd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.50 (dd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.33 (s, 2H), 5.28 (s, 2H), 4.89 (bs, 2H), 3.71 (s, 3H). MS: (calc.) 506.2; (obt.) 507.1 (MH)*	
205	346	O=\	ъ ъ		N{2-Amino-phenyl}- 84{6-bromo-4-oxo-4H-quinazolin-3-ylmethyl}-	56 (s, 1H), 3 Hz, 3 Hz, 1H), 1H), 7.96 8.0, 1.1 (s, 2H), (MH)⁺.	19

Ex.	pdo	M	<u>``</u>	2	Name	Characterization	Schm
206	278		Ŧ.			¹ H NWR: (DMSO) 8 (ppm): 9.63 (bs, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.8, 2.2 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.56 (dd, J = 8.2 Hz), 7.56 (dd, J = 8.2 Hz), 7.56 (dd, J =	. 01
3		z-z "z	5		benzo[d][1,2,3]tria 7.6 zin-3-ylmethyl}- 6.5 benzamide (bs,	7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.67 (s, 2H), 4.87 (bs, 2H). MS: (calc.) 449.0; (obt.) 450.0 (MH)*.	2
		o=			N(2-Amino-phenyl)- (m, 4-(6-chloro-4-oxo-	¹ H NMR: (DMSO) 8 (ppm): 9.63 (bs, 1H), 8.30-8.24 (m, 2H), 8.15 (ddd, J = 8.6, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2HH), 7.50 (d, J = 8.2 Hz, 2HH), 7.15 (d, J =	
207	348	Z-Z	 		4n- benzo[d][1,2,3]tria = 8.C zin-3ylmethyl} 2H), benzamide (MH)	8.0 Hz, 1H), 7.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.67 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 405.1; (obt.) 406.0 (MH)*	19
					enyl}-	H. NMR (acetone-d ₆) 8 (ppm): 9.07 (bs, 1H), 8.02 (d, J=8.2 Hz, 2H), 7.64-7.44 (m, 3H), 7.33 (dd, J=7.8, J	
508	349	γ _γ γ _γ Σ Ι	- -	ᆼ	pyridinyl-amino)- methyll-benzamide = 7 336	= 8.0, 1.4 Hz, 1H), 6.78 (bs, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.48 (dd, J = 8.1, 2.6 Hz, 1H), 6.16 (dd, J = 7.7, 2.5 Hz, 1H), 4.76-4.55 (m, 4H). HRMS (calc.): 336.1386, (found): 336.1389.	7
٥٥٥	350	, u	7		N(2-Amino-phenyl)- sys 4-[(3,4,5-trifluoro- 7,6	¹ H NMR (acetone-d ₆) δ (ppm): 9.06 (bs, 1H), AB system ($\delta_A = 8.02$, $\delta_B = 7.56$, $J = 8.3$ Hz, 4H), 7.74-7.55 (m, 1H), 7.33 (d, 1 – 8.0, 1H), 7.03 (td, 1 – 7.5)	-
503	3	F N N 35-		5	2-pyridinyl-amino} 1.5 methyll-benzamide Hz,	2-pyridinyl-amino} 1.5 Hz, 1H), 6.96-6.83 (m, 2H), 6.71 (td, J = 7.6, 1.4 methyl]-benzamide Hz, 1H), 4.74 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H).	:

EX.	Cpd	M	>	7	Name	Characterization	Schm
210	351	S N N I	-		N-(2-Amino-phenyl)- 14 4-(2,4-dioxo-1,4-5.,2 dihydro-2H-8,2 thieno[3,2-2H dlpyrimidin-3-77,3 ylmethyl)-39	δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 1.4), J = 7.1 Hz, 1H), 6.98-6.94 (m, 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 1.4), 6.58 (dd, J = 7.1, 1.4), 4.88 (bs, 2H). MS: (calc.) (MH) ⁺ .	
211	352	Ph N N	НЭ. НЭ		N-{2-Amino-pheny }- (m 4-{5-phenyl- [1,2,4]oxadiazol-3- y }-benzamide (ca	N{2-Amino-phenyl}- (m, 6H), 7.79-7.66 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 4.5-phenyl- (7.00 (dd, J = 7.3, 7.3 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.3, 7.3 Hz, 1H), 4.96 (bs, 2H). MS: (calc.) 356.1; (obt.) 357.0 (MH)*.	50
212	353	Me O N	СН		N-(2-Amino-phenyl)- (m 4-(5-methyl- 11,2,4)oxadiazol-3- 77.5 yl)-benzamide (ca	¹ H NMR: (DMSO) δ (ppm): 9.81 (bs, 1H), 8.17-8.11 (m, 4H), 7.18 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (bs, 2H), 2.70 (s, 3H). MS: (calc.) 294.1; (obt.) 295.0 (MH) ⁺ .	50
213	354	N N N N N N N N N N N N N N N N N N N	СН		N-(2-Amino-phenyl)- 4H 4-(5-piperidin-1- 1H ylmethyl- 1H [1,2,4]oxadiazol-3- 1.(yl)-benzamide 37	1H NMR: (acetone) 5 (ppm): 9.29 (bs, 1H), 8.21 (m, 4H), 7.31(d, J = 8.0Hz, 1H), 7.03(dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.68 (bs, 2H), 3.94 (s, 2H), 2.58 (t, J = 5.1 Hz), 1.63-1.55 (m, 4H), 1.47-1.43 (m, 2H). MS (Calc) 377.2; (Obt.) 378.3(MH)+	50
214	355	Z Z O Z Z O Z Z O Z Z Z O Z Z Z O Z Z Z O Z	<u> </u>	유	N-(2-Amino-phenyl)- 4H 4-(5-morpholin-4- 1H ylmethyl- Hz [1,2,4]oxadiazol-3- 2.6 yl)-benzamide (MI	1H NMR: (acetone) 5 (ppm): 9.28 (bs, 1H), 8.21 (m, 4H), 7.31(d, J = 8.1 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.67 (bs, 2H), 4.01 (s, 2H), 3.66 (t, J = 4.8Hz), 2.65 (t, J = 4.4 Hz). MS: (Calc.) 379.2; (Obt.): 380.2 (MH)+	50

E.	Cpd	M	_	7	Name	Characterization	Schm
215	356	H ₃ C C N	СН		N-(2-Amino-phenyl)-7, 4-(5-propyl-11, 2, 4] oxadiazol-3-11 ylmethyl)-2 benzamide 7,	¹ H NMR: (DMSO) 6 (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.88 (s, 2H), 4.16 (s, 2H), 2.87 (t, 7.0, 2H), 1.72 (q, J = 7.5 Hz, 2H), 0.92 (t, J = 7.0 Hz, 3H). (MH)*: 337.2.	50
216	357	N.O.N.	СН	СН	N(2-Amino-phenyl)- 1, 4(5-pyridin-3-yl- 8, [1,2,4]oxadiazol-3- Hylmethyl)- benzamide H	¹ H NMR: (DMSO) 5 (ppm): 9.64 (s, 1H), 9.24 d, J = 1.8 Hz, 1H); 8.86 (dd, J = 1.3 Hz, J = 4.8 Hz, 1H), 8.45 (dd, J = 1.8 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.66 (dd, J = 4.8 Hz, J = 7.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.89 (s, 2H), 4.31 (s, 2H). (MH)*.372.3.	50
217	358	NO N	сн сн	CH	N-(2-Amino-phenyl)- 4-(5-pyridin-4-yl- [1,2,4]oxadiazol-3- ylmethyl)- benzamide	l, J = Hz, r, 1H),), 4.89	50
218	359	NC HN S	. В	Ж	4(5-Acetylamino-4-11 cyano-thiophen-2-6 ylmethyl-N42-6 amino-phenyl)-1 benzamide (s	s, 1H), 9.60 (bs, (d, J = 8.1 Hz, 2H), = 7.3 Hz, 1H), Hz, 1H), 6.591 (dd, 4.13 (s, 2H), 2.17 (found).	49
219	360	Ph HN S hy	당	В	4-(5-Benzoylamino- 1 4-cyano-3-methyl- 7 thiophen-2- = ylmethyl-N-(2- 7 amino-phenyl- H	1H NMR (DMSO) 8 (ppm): 11.77 (s, 1H), 9.61 (s, 1H); 7.93 (d, J = 7.0 Hz, 4H), 7.52-7.63 (m, 3H), 7.38 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.89 (s, 2H), 4.15 (s, 2H), 2.24 (s, 3H). (MH)*: 467.0	49

Ex.	Cpd	M	>	2	Name Characterization		Schm
220	361	HN S TY	Н		N-(2-Arnino-phenyl)- 4-(4-cyano-3- methyl-5-(3-phenyl- fureido)-thiophen-2- ylmethyl]- benzamide N-(2-Arnino-phenyl- 6-1, 7.16 (d, yle 8.2 Hz ylmethyl)- 2H), 4.08 (s, zho enzamide	δ (ppm): 10.12 (s, 1H), 9.61 (s, 1H), (d, J = 7.6 Hz, 2H), 7.27-7.43 (m, 6.54, 1H), 6.93-7.05 (m, 2H), 6.77, 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2.19 (s, 3H). (MH)*: 482.4	49
221	362	0 - N	СН		N-(2-Amino-phenyl)- 4-(3-oxo-2,3- dihydro- benzo[1,4]oxazin- Hz, 1H), 6.92 4-ylmethyl)- benzamide 4-(3-oxo-2,3- 4-(3-0xo-2,3- 4-	N-(2-Amino-phenyl) 14 NMR: (DMSO) & (ppm): 9.60 (s, 1H), 7.92 (d, J = 4(3-oxo-2,3-4(3-oxo-2,3-4), 7.40 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92-7.04 (m, 5H), 6.75 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 6.57 (td, J = 7.4 Hz, 1.4 Hz, 1H), 5.24 (s, 2H), 4-ylmethyl) 4.88 (bs, 2H); 4.82 (s, 2H). (MH)*: 374.1	11
222	363	O No	С	СН	N-(2-Amino-phenyl)- ¹ H NMR: (DMSO) & 4(3-oxo-2,3-	N-(2-Amino-phenyl)- ¹ H NMR: (DMSO) & (ppm): 9.58 (s, 1H), 7.90 (d, J = 4(3-oxo-2,3-8.2 Hz, 2H), 7.42 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.19-7.11 (m, 3H), 7.04-6.92 benzo[1,4]thiazin- (m, 2H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (td, J = 8.0 Hz, 1.6 Hz, 1H), 5.31 (s, 2H); 4.88 (bs, 2H); 3.70 (s, 2H): (MH)*: 390.1	11
223	364		공	공	N-(2-Amino-phenyl)- ¹ H NMR: (DM 4-(3-0xo-2,3-dihydro-pyrido[3,2-3H), 7.15 (d., b][1,4]oxazin-4-(dd, J= 7.6, ylmethyl)- 6.58 (dd, J= benzamide 2H), 4.87 (s., z.)	N-(2-Amino-phenyl)- ¹ H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 7.98 (d, J = 4.3-oxo-2,3- 4.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.45-7.40 (m, dihydro-pyrido[3,2-3H), 7.15 (d, J = 8.2 Hz, 1H), 7.09-7.05 (m, 1H), 6.96 b][1,4]oxazin-4 (dd, J = 7.6, 7.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 7.6, 7.6 Hz, 1H), 5.31 (s, 2H), 4.90 (bs, benzamide 2H), 4.87 (s, 2H). (MH) ⁺ : 375.1	11
224	365	O TO HO	늉	끙	N(2-Amino-phenyl)- 8.2 Hz, 2H), 7 4-(1-hydroxy-3-oxo- 7.24 (d, J = 7 indan-2-ylmethyl)- (d, J = 8.2 Hz benzamide = 7.0 Hz, 1H) 3.21-3.30 (m,	N{2-Amino-phenyl}- 8.2 Hz, 2H), 7.73-7.84 (m, 3H), 7.53-7.62 (m, 3H), 4(1-hydroxy-3-oxo-7.24 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.85 indan-2-ylmethyl}- (d, J = 8.2 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 5.27 (t, J = 6.4 Hz, 1H), 4.95 (s, 2H), 3.21-3.30 (m, 1H), 3.11-3.13 (m, 2H). (MH)*: 373.1	46

Ex.	Cpd	W	>	7	Z Name Cha	Characterization	Schm
225	366	25.50 V	СН	끙	N(2-Amino-phenyl)- 8.8 4-phenoxy- 6H), benzamide 6.55	¹ H NMR: (DMSO) & (ppm): 9.61 (s, 1H); 8.01 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.06-7.24 (m, 6H), 6.97 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H). (MH)⁺: 305.0	1
226	367	Meo Const.	СН		M: (2-4-methoxy-4-5-(4-methoxy-4-5-(4-methoxy-4-5-6-1), 6.5-6-1), 6.5-6-1), 6.5-6-1), 6.5-6-1), 6.5-6-1), 6.5-6-1), 6.5-6-1)	M-(2-Amino-phenyl)- ¹ H NMR (CDCl ₃) & (ppm): 8.77 (s,1H), 7.93 (d, J = 4-[5-(4-methoxy-8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38-6.98 (m, 4H), 3.81 dihydro-furan-2-yl]- (s, 3H).	52
230	371	MeO O N N N O Ne	GH.	GH	M(2-Amino-phenyl)- ¹ H N 4-[1,3-bis-(3,4- dimethoxy-phenyl)- 7.39 ureidomethyl]- 2.2, benzamide 5.01	N42-Amino-phenyl)- ¹ H NMR (DMSO-d ₆): \$ 10.08 (brs, 1H), 7.99 (d, J = 4-[1,3-bis-(3,4- 7.9 Hz, 2H), 7.70 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), dimethoxy-phenyl)- 7.39-7.33 (m, 1H), 7.30-6.90 (m, 7H), 6.87 (dd, J = 2.2, 8.35 Hz, 1H), 6.78 (dd, J = 2.2, 8.35 Hz, 1H), benzamide 5.01 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H).	57
231	372	CI CI OME	СН		N-(2-Amino-phenyl)- 4-[3-(4-chloro-phenyl)-1-(3,4-7.16-dimethoxy-phenyl)-6.75 ureidomethyll-benzamide	M{2-Amino-phenyl} 'H NMR (CDCI ₃): \$ 8.02 (brs, 1H), 7.90 (d, J = 7.9 4-[3{4-chloro-phenyl} 'L', 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.42-7.24 (m, 6H), 7.16 (t, J = 7.5 Hz, 1H), 6.91 (brd, J = 5.71 Hz, 3H), 6.75 (brd, J = 8.3 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 4.99 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H).	57
232	373	N OME	СН	СН	M{2-Amino-phenyl}- 1H N 4-[1-{3,4- dimethoxy-phenyl}- J = 3-phenyl- ureidomethyl}- 6.94 benzamide	M{2-Amino-phenyl}- 4-[1-{3,4- 7.9 Hz, 2H), 7.88 (s, 1H), 7.80-7.72 (m, 1H), 7.50 (dd, dimethoxy-phenyl}- 3-phenyl- ureidomethyl]- benzamide M(2-Amino-phenyl) 7.99 (d, J = 4-11-43,4- 7.9 Hz, 2H), 7.80 (dd, J = 7.9 Hz, 1H), 7.30- 6.94 (m, 7H), 6.78 (d, J = 6.6 Hz, 1H), 5.03 (s, 2H), benzamide	57

_	200	>	>	7	Nomo		
					M2-Amino-nhenvll.		Schm
					4-[1-(3,4-dimethoxy,n)	4-[1-(3,4- Hz, 2H), 7-49 (d, J = 8.35 Hz, 2H), 7-43-7.32 (m, 5H), dimethoxyabond 2 10.7 20.7 20.7 20.7 20.7 20.7 20.7 20.7 2	
(1)	374	O NH OME	ᆼ	ᆼ		8.35, 2.2 Hz, 3H), 6.94 (d, J = 7.5 Hz, 1H), 6.92 (d, J =	57
					phenyl}-	= 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (d,	
		Owe			<u></u>	J = 2.2 Hz, 1H), 6.34 (s, 2H), 5.02 (s, 2H), 3.98 (s,	
1					Biphenvl-4 4'-	3H), 3.87 (s, 3H).	
ന	375		2	5	cid	7.7	
,)	H. H.		5	bis-[(2-amino-	-	15
	+	τή)			phenyl)-amide]	Hz, 2H), 6.66 (dd, J=6.9, 7.7 Hz, 2H), 5.06 (bs, 4H).	
		Ι			N(2-Amino-phenyl)-	14-NMR (DMSO-d6), δ (ppm): 9.6 (bs, 1H), 8.32 (d,	
ന	377	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	Ę	근		33	
		-z \\/			_		13
		:				1H), 7.01 (dt, J=7.4, 7.7 Hz, 1H), 6.82 (d, J=7.9 Hz,	
	-				M.2.Amino phon.	111, 0.00-0.02 (III, 171, 4.98 (DS, 2H), 4.61 (d, 2H).	
		H ₃ C N S S			44.6-dimethyl-	44.6-dimethyl.	
\sim	378	-z	는 단 단		pvrimidin-2-	J=7.9 Hz, 2H), 7.61 (d, J= 7.9 Hz, 2H), 7.21 (d, J=7.9	-
		C			thvI).	Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J=7.9 Hz, 1H),	
,		5				6.64 (t, J=7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H).	
		1			Amino-phenyl)-	¹ H-NMR (DMSO-d6), 8 (ppm): 9.66 (bs, 1H), 9.07 (d.	
		LL				J=5.2 Hz, 1H), 7.97 (d, J=7.4 Hz, 2H), 7.78 (d, J=4.7	
~~	379	T S Z	SH SH		hyl-	Hz, 1H), 7.63 (d, J=7.4 Hz, 2H), 7.19 (d, J=7.7 Hz,	
		- Z	:			1H), 7.01 (dt, J= 7.4, 7.7 Hz, 1H), 6.81 (d, J=8.2 Hz.	
		·			ethyl)-	1H), 6.64 (dt, J=7.1, 7.4 Hz, 1H), 4.94 (bs, 2H), 4.57	
•	\dagger		1	7	benzamide ((s, 2H).	
		N. J.			Pvridine-2.5-	¹ H-NMR (DMSO-d6), δ (ppm): 10.23 (bs, 1H), 10.04	
	380	zir N			acid	(bs, 1H), 9.30 (s, 1H), 8.62 (dd, J=1.8, 8.0 Hz, 1H),	
	 3	-	ے۔۔۔ ح	 5		3.30 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.4 Hz, 1H), 7.24	_
		o }			_	d, J=7.4 Hz, 1H), 7.04 (dd, J=7.0, 14.0 Hz, 2H),	
	1			٦		6.90-6.83 (m, 2H), 6.74-6.63 (m, 2H), 5.11 (bs, 4H).	

Ex.	Cpd	M	<u> </u>	Z Name		Characterization	Schm
0	381	N S N	풍		nino-phenyl}- Jin-2- nylmethyl}- nide	H-NMR (DMSO-d6), 6 (ppm): 9.66 (bs, 1H), 8.52 (bs, 1K2-Amino-phenyl)- 1H), 7.96 (d, J=7.4 Hz, 2H), 7.69 (d, J=5.8 Hz, 1H), 7.59 (d, J=7.4 Hz, 2H), 7.38 (d, J=7.7 Hz, 1H), 7.19 ylsulfanylmethyl)- (bs, 2H), 7.00 (d, J=6.9 Hz, 1H), 6.83 (d, J=6.9 Hz, 1H), 6.84 (dd, J=6.7, 7.2 Hz, 1H), 4.94 (bs, 2H), 4.55 (b+s, 2H).	11
241	382	H ₃ C N N S ² C		M(2- 4-[(4 CH. pyrin ylam benz	N(2-Amino-phenyl)- 1 4-[(4,6-dimethyl- J pyrimidin-2- F ylamino)-methyl]- 1 benzamide 1	N42-Amino-phenyl)	33
242	383		. В	CH 4-[(4 pyric meth	N(2-Amino-phenyl)- 4-{(4,6-dimethyl- pyridin-2-ylamino)- methyl]-benzamide	¹ H-NMR (DMSO-d6) , δ (ppm): 9.66 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.50 (d, J=8.2 Hz, 2H), 7.96 (d, J= 7.9 Hz, 1H), 7.01 (dd, J=7.7, 7.4 Hz, 1H), 6.82 (d, J= 7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.33 (s, 1H), 6.25 (s, 1H), 4.58 (d, J=4.4 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H).	33
243	384			M.2-Amino-1 4-(4,6-dimet CH CH pyrimidin-2- yloxymethyl benzamide	ohenyl)- thyl-)-	M2-Amino-phenyl)- ¹ H-NMR (DMSO-d6), δ (ppm): 9.58 (bs, 1H), 7.88 (d, 4(4,6-dimethyl- 1=5.8 Hz, 2H), 7.46 (d, 1=8.2 Hz, 2H), 6.90-6.81 (m, pyrimidin-2- 1H), 6.68 (d, 1=7.9 Hz, 1H), 6.50 (t, 1= 7.4 Hz, 1H), 6.40-6.38 (m, 1H), 6.29-6.26 (m, 1H), 5.33 (s, 2H), benzamide 2.25 (s, 6H).	11
244	385	O Z Z Z		托	N-(2-Amino-phenyl)- 4-[(6-methoxy- pyrimidin-4- ylamino)-methyl]- benzamide	¹ H-NMR (DMSO-46), 8 (ppm): 9.64 (bs, 1H), 8.21 (bs, 1H), 7.95 (d, J=7.96 Hz, 2H), 7.83 (d, J=5.8 Hz, 1H), 7.44 (d, J=7.9Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.00 (dd, J= 7.4, 7.7 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.64 (d, J=7.1 Hz, 1H), 4.96 (bs, 2H), 4.58 (bs, 2H), 3.81 (s, 3H).	33

Ē					
Schm		33	33	33	37
Characterization	¹ H-NMR (DMSO-d6) , 8 (ppm): 9.79 (bs, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.96 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4Hz, 1H), 7.02 (dd, J=7.1, 7.7 Hz, 1H), 6.83 (d, J=7.7 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.59 (bs, 2H), 2.52 (bs, 3H).			N-(2-Amino-phenyl)- 1	M(2-Amino-phenyl)- J=7.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.37-7.30 (m, 1H), 4-1(6-methoxy- 7.25-7.21 (m, 2H), 7.19-6.99 (m, 1H), 6.84-6.81 (m, pyridin-2-ylamino)- 1H), 6.67-6.64 (m, 1H), 6.11-6.07 (m, 1H), 5.93-5.89 methyl]-benzamide (m, 1H), 4.93 (bs, 2H), 4.56 (d, J=5.8 Hz, 2H), 3.80 (s,
Name	4-[(6-Acetyl-benzo[1,3]dioxol-5-CH ylamino)-methyl]-N-(2-amino-phenyl)-benzamide	N-(2-Amino-phenyl)- 4-[(4-chloro-6- methoxy-pyrimidin- 2-ylamino)-methyl]- benzamide	N-(2-Amino-phenyl)- 4-[(2,6-dimethoxy- pyridin-3-ylamino)- methyl]-benzamide	N-(2-Amino-phenyl)- 4-[(1 H- benzoimidazol-2- ylamino)-methylj- benzamide	N(2-Amino-phenyl)- 4-[(6-methoxy- pyridin-2-ylamino)- methyl]-benzamide
7	끙		Ж	КЭ	нэ
>	당	СН	СН	CH.	НЭ
M	O O CH ₃	H ₃ C _O N N N S ²	H ₃ C O H	H H H H	H ₃ C _O N H Sc _o N
Pd	386	387	388	389	390
Ex.	245	246	247	248	249

EX.	Cpd	W	Υ	7	Z Name	Characterization	Schm
250	391	N S S	СН		N{2-Amino-phenyl}-4-(quinolin-8-ylsulfanylmethyl)-benzamide	¹ H-NMR (DMSO-d6) , δ (ppm): 9.68 (bs, 1H), 8.95 (bs, 2H), 8.43-8.38 (m, 1H), 7.90 (bs, 2H), 7.80-7.55 (m, 6H), 7.22 (d, J= 7.7 Hz, 1H), 7.03 (d, J= 7.7 Hz, 1H), 6.63 (d, J=7.4 Hz, 1H), 5.05 (bs, 2H), 4.48 (d, J=7.7, 2H).	11
251	392	H ₃ C ^O N V V V V V V V V V V V V V V V V V V	공	СН	M(2-Amino-phenyl)- 4-[(2,6-dimethoxy- pyrimidin-4- ylamino)-methyl]- benzamide	¹ H-NMR (DMSO-d6) , δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.84 (t, J=5.9 Hz, 1H), 7.46 (d, J=7.46 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.04 (d, J=6.6 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.64 (dd, J=7.7, 7.4 Hz, 1H), 5.51 (bs, 1H), 4.57 (bs,, 2H), 3.82 (s, 3H), 3.84 (s, 3H).	37
252	393	H ₃ C ^{-O} H H H H H H H H H H H H H H H H H H H	СН		M{2-Amino-phenyl}- 4-(3,5-dimethoxy- benzylamino)- benzamide	H-NMR (DMSO-d6), 8 (ppm): 9.63 (bs, 1H), 7.79 (d, 1/4.2-Amino-phenyl)- J=8.5 Hz, 2H), 7.19 (d, J=6.6 Hz, 1H), 7.00 (dd, 4/3.5-dimethoxy- J=7.9, 7.1 Hz, 1H), 6.62 (t, J=6.0 Hz, 1H), 6.82 (dd, J=1.4, 7.9 Hz, 1H), 6.67 (d, J= 8.8 Hz, 2H), 6.58 (bs, 2H), 6.42 (bs, 1H), 4.87 (bs, 2H), 4.34 (d, J=6.0 Hz, 2H), 3.77 (s, 6H).	37
253	394	S YY	СН		N42-Amino-phenyl)- 443-methoxy- phenylsulfanylmeth yl)-benzamide	Mt2-Amino-phenyl)- J=7.9 Hz, 2HJ, 7.55 (d, J=8.2 Hz, 2H), 7.29-7.20 (m, 4-(3-methoxy-2H), 7.02-6.95 (m, 2H), 6.84-6.79 (m, 1H), 6.67-6.62 (m, 1H), 6.57-6.54 (m, 1H), 6.44-6.41 (m, 1H), 4.93 (bs, 2H), 4.41 (bs, 2H), 3.79 (s, 3H).	11
254	395	H ₃ C ⁻⁰ CH ₃	СН СН		N{2-Amino-phenyl}-4{3,5-dimethoxy-phenoxymethyl}-benzamide	¹ H-NMR (DMSO-d6) , δ (ppm): 9.72 (bs, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=6.9, 7.1 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (dd, J= 7.4, 7.7 Hz, 1H), 6.27 (s, 2H), 6.26 (s, 1H), 5.23 (s, 2H), 5.21 (bs, 2H), 3.77 (s, 6H).	11

Ex.	Cpd	W	>	Z	Z Name	Characterization	Schm
255	396	0 =Z	H)	끙	nino-phenyl)- olin-2- ethyl}- nide	16), 8 (ppm): 9.70 (bs, 1H), 8.35 (d, 5 (d, J=7.9 Hz, 2H), 7.96 (d, J=7.9 =8.2 Hz, 1H), 7.76-7.69 (m, 2H), 1 Hz, 1H), 7.24-7.16 (m, 2H), 7.02 (1H), 6.83 (d, J=8.2 Hz, 1H), 6.66 (s, 2H), 4.94 (hs, 2H)	=======================================
256	397	H ₃ C [*] O H L ₃ C O CH ₃ .	СН	끙	N-(2-Amino-phenyl)- 4-[(3,5-dimethoxy- phenylamino)- methyl]-benzamide	14-NMR (DMSO-d6), δ (ppm): 9.62 (bs, 1H), 7.96 (d, 142-Amino-phenyl)- J=7.9 Hz, 2H), 7.49 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 4-{(3.5-dimethoxy-Hz, 1H), 7.00 (dd, J=7.5, 7.9 Hz, 1H), 6.81 (d, J=7.9 phenylamino)- Hz, 1H), 6.63 (dd, J= 7.0, 8.0 Hz, 1H), 5.78 (s, 2H), methyll-benzamide 5.76 (s, 1H), 4.92 (bs., 2H), 4.35 (d, J=5.7, 2H), 3.65 (s, 6H).	33
. 257	398	NH ₂	СН	Z	bis(M2-Amino-phenyl)-incotinamide)-6-disulfide	¹ H-NMR (DMSO-d6), 5 (ppm): 9.82 (bs, 2H), 9.08 (bs, 2H), 8.34 (d, J=8.3 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 7.01 (dd, J=6.3, 7.0 Hz, 2H), 6.80 (d, J=7.9 Hz, 2H), 6.61 (t, J=7.03 Hz, 2H), 5.05 (bs, 4H).	
258	399	=Z /Ş-	СН	НЭ	M(2-Amino-phenyl)- 7 4-(isoquinolin-1- ylaminomethyl)- 7 benzamide (¹ H-NMR (DMSO-d6), δ (ppm): 9.90 (bs, 1H), 8.16 (bs, 2H), 7.65 (d, J=4.8 Hz, 2H), 7.54 (bs, 2H), 7.25 (d, J=7.0 Hz, 2H), 7.11 (bs, 2H), 7.07-7.02 (m, 2H), 6.84 (d, J=7.9 Hz, 1H), 6.67 (bs, 1H), 5.01 (bs, 2H), 4.88 (bs, 2H).	33
259	400	HN Y	ъ Н	픙	NK2-Amino-phenyl)- 4-[(2,3-dihydro- benzo[1,4]dioxin-6- ylamino)-methyl]- benzamide	N42-Amino-phenyl)- 14-NMR (DMSO-d6), 8 (ppm): 9.66 (bs, 1H), 7.97 (d, 4-{(2,3-dihydro- J=7.0 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.22 (d, J=7.5 benzo[1,4]dioxin-6- Hz, 1H), 7.02-6.97 (m, 1H), 6.84 (bs, 1H), 6.82-6.71 ylamino)-methyl]- (m, 2H), 6.16 (d, J=6.6 Hz, 1H), 6.08 (s, 1H), 4.32 (bs, benzamide 2H), 4.16-4.13 (m, 4H).	33

Ex.	Cpd	M	<u>></u>	7	Z Name Characterization	Schm
260	401	H ₃ C N S	СН		4-[(4-Acetylamino-1H), 7.97 (d, J=7.9 Hz, 2H), 7.53 (d, J=7.9 Hz, 2H), 7.53 (d, J=7.9 Hz, 2H), 7.22 (d, J=7.9 Hz, 1H), 7.02 (t, J=7.9 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.65 (t, J=7.5 hz, 1H), 6.55 (d, J=8.3 Hz, 2H), 4.98 (bs, 2H), 4.38 (bs, 2H), 2.00 (s, 3H).	9.56 (bs, z, 2H), 1), 7.02 (t, t, J=7.5), 4.38
261	402	IN N	СН		H-NMR (DMSO-46), 5 (ppm): 9.65 (bs, 1H), 7.98 (d, 14; Amino-phenyl) J=7.9 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.5 4-{(4-morpholin-4-Hz, 1H), 6.78 (d, J=8.8 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), methyl-benzamide 6.55 (d, J=8.8 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 4.94 (bs, 2H), 4.94 (bs, 2H), 4.95 (d, J=6.7 Hz, 4H).	7.98 (d, d, J=7.5 1, J=7.9 5 Hz, 1H), 1, J=5.7 4 Hz, 4H).
262	403	CH3 H 13C 20 25 CH3 H 13C 20 25 CH3	СН		M(2-Amino-phenyl)	7.96 (d, d, J=8.2 J=8.2 Hz, 94 (bs, 23 (s, 3H).
263	404	H ₃ C _C	СН СН		N4(2-Amino-phenyl)	, 7.98 (d, (d, J=7.9 7.9 Hz, 3 (bs, 2H),
264	405	N CH CH	ن		##•NMR (DMSO-d6), 5 (ppm): 9.62 (s, 1H), 8.72 (s, 1H), 8.49 (d, J = 10.1 Hz, 1H), 7.93 (d, J = 7.9 Hz, 2H), 4-{[4-methoxy-3-7.68 (d, J = 6.6 Hz, 1H), 7.37 (d, J = 7.5 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.62 (d, J=7.5 hz, 1H), 6.63 (d, J=7.5 hz, 1H), 6.69 (J=8.8 Hz, 1H), 6.69 (J=8.8 Hz, 1H), 9.61 (5.76 (s, 1H), 4.64 (bs, 4H), 3.62 (s, 3H).	8.72 (s, 9 Hz, 2H), 2H), 7.16 78 (d; J (d, J=7.5 Hz, 1H),

Ex.	Cpd	M	Z λ	Name	Characterization	Schm
265	406	H ₃ C O N S Y H ₃ C O H	HO CH	2-[4-(2-Amino- phenylcarbamoyl)- benzylamino]-4,5- dimethoxy-benzoic acid	46, 3 (ppm): 9.67 (bs, 1H), 8.00 (d, 4 (d, J=7.9 Hz, 2H), 7.34 (s, 1H), 2H), 7.0 (t, J=7.9 Hz, 1H), 6.31 (s, 1H), 6.82 (d, 2 (t, J=7.9 Hz, 1H), 6.31 (s, 1H), 6.84), 3.75 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H)	33
266	407	H ₃ C N CH ₃	<u> </u>	Amino-phenyl)- ,5-dimethyl- iylamino)- iyl]-benzamide		33
267	408	IZ O	G G	N42-Amino-phenyl}- 4-{[4-{pyridin-3- ylmethoxy}- phenylamino}- methyl}-benzamide	8.72 (s, 7.97 (d, (d, J=8.3 lz, 1H), 6.70	33
268	409	H ₃ C		H-N (CH 4-[(2,4-dimethyl- J=7.7,1 bhenylamino)- J=9.1 methyl]-benzamide Hz, J=5.	.c. +.o. b	33
569	410	CH ₃ H N ² N ² CH ₃	<u>.</u> .	N.(2-Amino-phenyl)- 4-[(2,4,6-trimethyl- phenylamino)- methyl]-benzamide		33
270	411		В		3-D₆) δ *** (ππμ): 9.66 (s, H), 7.82 (m, 1H), 7.47 (d, J) 8.2 Hz, 1H), 7.03 (dd, J = J = 7.7 Hz, 1H), 6.65 (dd, J) s, 1H), 4.94 (s, 2H, NH ₂), 58 (m, 4H), 3.62 (m, 4H).	24, 33

Ex.	Cpd	W	<u> </u>	2	Name	Characterization	Schm
271	412	MeO H H H	СН		N-(2-Amino-phenyl)- 7.8 4-(3,4,5- trimethoxy- benzylamino)- benzamide 6.7	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.33 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.99 (m, 1H), 6.87 (dd, J = 6.0, 5.8Hz, 1H), 6.82 (m, 1H), 6.77 (s, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.64 (m, 1H), 4.87 (s, 2H, NH ₂), 4.32 (d, J = 5.5 Hz, 2H), 3.81 (s, 6H), 3.79 (s, 3H).	33
272	413	F H H	СН		N-(2-Amino-phenyl)- 7.7 4-(4-fluoro- 2H) benzylamino)- 8.0 benzamide 7.2	N{2-Amino-phenyl}- 7.79 (d, J = 8.7 Hz, 2H), 7.45 (dd, J = 5.8, 8.5 Hz, 4(4-fluoro-2H), 7.21 (m, 3H), 6.91 (m, 2H), 6.81 (dd, J = 1.1, 8.0Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.62 (dd, J = 1.0, 7.2 Hz, 1H), 4.86 (s, 2H, NH ₂), 4.39 (d, J = 6.0 Hz, 2H).	33
273	414	MeO H H	СН СН		N-{2-Amino-phenyl}-7.7 4-{4-methoxy-2H, benzylamino}-2H, benzamide Hz,	N-(2-Amino-phenyl)- 1.1. NMR (300 MHz, DMSO-de) 5 (ppm): 9.31 (s, 1H), 7.79 (dd, J = 1.1, 8.5 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.97 (m, 3H), 6.84 (m, 2H), 6.65 (m, 3H), 4.86 (s, 2H, NH ₂), 4.33 (d, J = 5.5 Hz, 2H), 3.58 (d, J = 1.6 Hz, 3H).	33
274	415	F H VY	Сн		N-(2-Amino-phenyl)- 7.9 4-[(4-fluoro- phenylamino)- 6.9 methylj-benzamide 1H)	(ppm): 9.66 (s, 1H), J = 8.0 Hz, 2H), 7.21 =1.6, 7.1, 8.2 Hz, 1H), 3 (dd, J =1.1, 8.0 Hz, 2 Hz, 1H), 4.94 (s, 2H,	33
275	416	, NH NH	CH	끙	N(2-Amino-phenyl)- 7.7 4-(3-fluoro-benzylamino)- 1.1 benzylamino)- 1H) benzamide 7.4	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.32 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.44 (m, 1H), 7.26 (m, 1H), 7.18 (dd, J = 1.4, 8.0 Hz, 2H), 7.12 (ddd, J = 1.7, 8.0, 8.2 Hz, 1H), 6.99 (m, 2H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.67 (dd, J = 1.6, 8.8 Hz, 2H), 6.62 (dd, J = 1.4, 7.4 Hz, 1H), 4.87 (s, 2H, NH ₂), 4.45 (d, J = 6.0 Hz, 2H).	33

Cpd	M		\ \ \	7	Name	Characterization
		1	1			TH NMR (300 MHz DMSO-d-) & (ppm): 9 66 (c. 1 L)
	r de la companya de l			<u> </u>	N{2-Amino-phenyl}-	N-(2-Amino-phenyl)- 7.99 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.21
H) /1+				bhe	(0	$(M_1, M_2, M_3, M_4, M_3, M_4, M_4, M_5, M_4, M_5, M_4, M_5, M_5, M_5, M_5, M_5, M_5, M_5, M_5$
- F	me.	шеш	me_	<u>me</u>	methyl}-benzamide (6.46 (d, J = 8.2 Hz, 1H), 6.34 (m, 2H), 4.94 (s, 2H, NH), 4.41 (d. J = 6.0 Hz, 2H)
		Z	Z s	Z -	enyl)-	1H NMR (300 MHz, DMSO-De) & (ppm): 9.66 (s, 1H),
418 CH CH R	H H			jΕ	4-((4-chloro-6- methyl-nyrimidin-2-	
Z & Z				Ε 😤 .	amino)-methyl]- 7	ylamino}methyl}- 7.1, 8.0 Hz, 1H), 6.83 (dd, J = 1.5, 33
pe	aq	8 	a 	의	benzamide ((m, 2H), 4.94 (s, 2H, NH ₂), 4.61 (m, 2H), 2.3 2(s, 3H).
Ĭ.	JN.	<u>¥</u>	Ž	Ž	N-(2-Amino-phenyl)-	1 NMR (300 MHz, DMSO-De) & (ppm): 9.69 (s, 1H),
O N N N N N N N N N N N N N N N N N N N				4-[(4		8.82 (m, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0
413 CH CH pyrin	5	5		ĕ.		(14, 14, 14, 14, 14, 14) $(1, 14, 14, 14)$ $(1, 14, 14, 14)$ $(1, 14, 14)$ $(1, 14, 14)$ $(1, 14, 14)$ $(1, 14, 14)$ $(1, 14, 14)$ $(1, 14, 14)$
Ci Sylan	Ci	yiai	yian	ylan ben	ylalnıno)-metnyij- benzamide	6.67 (m, 1H), 5.0 (bs, 2H, NH ₂), 4.60 (d, $J = 6.3 \text{ Hz}$,
N42	N-(2)	N-(2)	N-(2	72	N-(2-Amino-phenyl)-	
		<u>\$</u>	2	2	9	¹ H NMR (300 MHz, DMSO-D ₆) 8 (ppm); 9.87 (s. 1H).
Y N N				<u>ஓ</u>		
H H	H H	<u>ਲ</u>		툿	-fouir	
JA J	Nd O	<u>a</u>	<u>8</u>	줅.		Hz, 1H), 6.66 (dd, J = 7.1, 8.0 Hz, 1H), 5.86 (bs. 1H).
yla	yla	yla	yla ber	열	ylamino}-methyl)- 4 benzamide	4.95 (s, 2H, NH ₂), 4.51 (m, 2H).
			_			¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9,66 (s. 1H).
-C-N	C/N	N-(2)	N-7.5	5	N-(2-Amino-nhenvi)-	7.99 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.50
, , , , , , , , , , , , , , , , , , ,				7.19	4-1(6-methoxy-	J = 2.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 7.9 Hz, 1H),
는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는	는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는 는	ა		. <u>`</u>	-{ou	7.12 (dd, J = 3.08 Hz, 8.79 Hz, 1H), 7.02 (dd, J = 7.0 33
MeO N	ż		3 2	ž, e		, 7.5 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (m,
					N 3	ZH), 6.15 (t, J = 6.16 Hz, 1H), 4.94 (s, ZH, NH ₂), 4.39
					וו	(u, J = 0.13 Hz, 2HJ, 3.73 (S, 3H).

Ex.	Cpd	W		7	Name	Characterization	Schm
	422	F ₃ CO	СН		N.(2-Amino-phenyl)- $\frac{^{1}H}{7.99}$ 4-[(4, J. trifluoromethoxy- $\frac{^{1}J}{J}=\frac{7}{7}$ phenylamino)- $\frac{^{1}J}{J}=\frac{7}{7}$ methyl]-benzamide $\frac{^{1}J}{4.42}$, DMSO-d ₆) & (ppm): 9.66 (s, 1H), z, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 , 7.09 (d, J = 9.1 Hz, 2H), 7.03 (dd, H), 6.83 (d, J = 8.0 Hz, 1H), 6.71 (t, 63-6.67 (m, 3H), 4.94 (s, 2H, NH ₂), z, 2H).	33
282	423	OCF ₃	НО	· HO	N.(2-Amino-phenyl)- ¹ H N 4-[(3- trifluoromethoxy- phenylamino)- methyll-benzamide [2H),	N-(2-Amino-phenyl)- ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.67 (s, 1H), 4-[(3-8.00 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.19 (m, 2H), 7.03 (ddd, J = 1.5, 8.0, 8.8 Hz, 1H), 6.85 (m, phenylamino)- 2H), 6.63 (m, 2H), 6.55 (s, 1H), 6.50 (m, 1H), 4.94 (s, methyl)-benzamide 2H, NH ₂), 4.44 (d, J = 6.0 Hz, 2H).	33
283a	424b	MeO OMe	СН	CH	14 N (2-Amino-phenyl)- (d, J 4-(13,4-dimethoxy-6.83 phenylamino)- (6.45 methyl]-benzamide Hz, J = (¹ H NMR (300 MHz, DMSO-d ₆) 5 (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.49 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NHz), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).	33
284	425	OCF ₃	СН	СН	N(2-Amino-phenyl)- 7.8C 4-(3- trifluoromethoxy- 6.96 benzylamino)- = 8. benzamide NH ₂)	¹ H NMR (300 MHz, DMSO-d ₆) 5 (ppm): 9.31 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.45-7.56 (m, 2H), 7.39 (s, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 6.96-7.03 (m, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 4.86 (s, 2H, NH ₂), 4.48 (d, J = 5.8 Hz, 2H).	33
285	426	F ₃ CO H	끙	СН	N(2-Amino-pheny:)- 7.79 4.4 trifluoromethoxy- 6.99 benzylamino}- 8.0, benzamide 4.45	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 1.4, 7.7 Hz, 1H), 6.99 (ddd, J = 1.4, 8.0, 8.5 Hz, 2H), 6.81 (dd, J = 1.4, 8.0, 8.5 Hz, 2H), 6.81 (dd, J = 1.4, 8.0, 8.5 Hz, 2H), 4.85 (s, 2H, NH ₂), 4.45 (d, J = 6.0 Hz, 2H).	33

<u>Σ</u>	Pg C	A		7	Namo		٢
286	427	MeO Y	. 공	T -	nino-phenyl)- ethoxy- amino)- benzamide	Schm (s, 1H), 7.4, 8.0 (m, 2H), 33 (m, 2H), 36 (d, J =	E
287	428	IN O	СН	CH (be	1. NMR (300 MHz, DMSO-d ₆) S (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.0 Hz, 1H), 6.683 (d, J = 7.5 Hz, 1H), 6.63-6.69 (m, 2H), 6.33 (d, J = 5.4 Hz, 1H), 6.15 (t, J = 6.16 Hz, 1H), 6.04 (dd, J = 5.2 Hz, 1H), 5.86 (s, 2H), 4.94 (s, 2H, NH ₂), 4.35 (d, J = 6.16 Hz, 2H).	(s, 1H), , 2H), 7.21 ; 1H), 6.33 (d, J = 4 (dd, J = NH ₂), 4.35	
288	429	OMe	СН		14 NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.63 (s, 1H), 7.22 Amino-phenyl)- 7.90 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.02 (ddd, J = 1.4, 7.1, 8.0 Hz, 1H), 6.86 (m, 2H), 6.56-6.75 (m, 3H), 6.43 (dd, J = methyll-benzamide 1.6, 7.7 Hz, 1H), 5.75 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH ₂), 4.47 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H).	(s, 1H), 2H), 7.22 3.0 Hz, 1d, J = 33 (s, 2H,	
586	430	N OMe	S HS	CH 4-150	H. NMR (300 MHz, DMSO-46) 5 (ppm): 9.61 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (dd, J = 1.1, 7.7 Hz, 1H), 6.97-7.05 (m, 2H), 6.82 (dd, J = 1.2, 8.1 Hz, 1H), 6.46 (ddd, J = 1.4, 7.7, 8.0 Hz, methyll-benzamide IH), 6.41 (t, J = 6.3 Hz, 1H), 6.16-6.25 (m, 3H), 4.93 (s, 2H, NHz), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H).	(s, 1H), 2H), 7.21 6.82 (dd, 8.0 Hz, H), 4.93 ;, 3H).	
290	431	F ₃ C → H	<u></u>		N-(2-Amino-phenyl) 1.1.53 (s, 1H), 8.08 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.8 4(2,2,2-trifluoro-Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.0, 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.0, 7.0, 7.6 Hz, 1H), 4.96 (s, 2H, NH ₂).	3 (s, 1H), 1, J = 8.8 = 7.0, d, J = .	Γ

Ex.	Cpd	M	_	Z	Z Name (Characterization	Schm
291	432	MeO OMe			nino-phenyl)- loro-6- trimethoxy- amino}- lin-2- b]-methyl}-	N-(2-Amino-phenyl) -	24, 33
292	433	MeO H H MeO OMe CI	СН		N(2-Amino-phenyl)- 4-[4-chloro-6- (3,4,5-trimethoxy- phenylamino)- pyrimidin-2- ylaminol-methyl}- benzamide	¹ H NMR (300 MHz, DMSO-d _s) δ (ppm): 9.65 (s, 1H), 9.43 (s, 1H), 7.97 (m, 3H), 7.46 (bs, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (m, 3H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.08 (s, 1H), 4.93 (s, 2H, NH ₂), 4.69 (bs, 2H), 3.65 (s, 9H).	24, 33
293	434	MeO OMe	СН		N(2.Amino-phenyl)- 4(3,4-dimethoxy- benzylamino)- benzamide	¹ H NMR (300 MHz, DMSO-d ₆) & (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.04 (s, 1H), 6.92-7.01 (m, 3H), 6.80-6.87 (m, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.62 (m, 1H), 4.87 (s, 2H, NH ₂), 4.32 (d, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H).	33
294	435	N N N N N N N N N N N N N N N N N N N	ਲ ਲ		N-{2-Amino-phenyl}- 7 4-{(4-morpholin-4- 7 yl-pyrimidin-2- 7 ylamino)-methyl]- H benzamide	N-(2-Amino-phenyl)- 7.95 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.31 (bs, 1H), 7.21 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.0 Hz, 1H), 6.09 (d, J = 6.2 hz, 2H), 4.54 (d, J = 5.7 Hz, 2H), 3.67 (s, 4H), 3.53 (s, 4H).	24, 1, 33

EX.	Cpd	M	>	2	Name Characterization	Cohm
295	436	I N	<u>ਲ</u> ਲ		nino-phenyl)- H-indol-3-yl)- nino]- I-benzamide), 2, 2, 1), 57
596	437	Mes Mes	СН		N(2-Amino-phenyl)- 1 H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.67 (s, 1H), 4-[(4-7.99 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.03 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.53 (m, 4H), 4.95 (s, 2H, NH ₂), 4.41 (d. J = 5.7 methyll-benzamide Hz, 2H), 2.37 (s, 3H)	33
297	438	SMe	생 당		N{2-Amino-phenyl} 1 H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 4-{(3-7.99 (d, J = 7.5 Hz, 2H), 7.03 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 6.83 (d, J = 7.9 phenylamino) Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.39-6.51 (m, 4H), 4.94 (s, 2H, NH ₂), 4.41 (d. J = 5.7 Hz, 2H), 2.42 (s, 3H).	6: -
298	439	MeO MeO CI NI	<u>ਲ</u> ਲ		N42-Amino-phenyl)-	15, 32 33
299	440	MeO NI	- 등	CH OH N	N{2-Amino-phenyl}	59 1, 15, 1, 10, 33

EX.	Cpd	M	_	2	Name Characterization		Schm
300	441	H ₃ C O H O H O H O H O H O H O H O H O H O	К	СН	4-[(2-Acetyl-4,5-9,45 (t, J = 5.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.54 dimethoxy-(d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.21 (d, J = 7.5 Hz, phenylamino)-Hz, 1H), 6.65 (dd, J = 6.6, 7.5 Hz, 1H), 6.83 (d, J = 7.5 methyll-N-(2-amino-Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.31 (s, 1H), phenyll-benzamide 4.95 (s, 2H, NH ₂), 4.63 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H).	.4	33
301	442	MeO OMe	СН	СН	N4(2-Amino-phenyl)- ¹ H NMR (300 MHz, CD ₃ 0D+CDCl ₃) & (ppm): 7.99 (d, 4{(4,3,4-1=7.9 Hz, 2H), 7.80 (d, J = 6.2 Hz, 1H), 7.76 (s, 1H), dimethoxy- 7.52 (d, J = 8.4 Hz, 2H), 7.27 (m, 1H), 7.14 (m, 1H), phenylamino}- 7.05 (dd, J = 2.2, 8.8 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), ylaminol-methyl}- 6.08 (d, J = 6.2 Hz, 1H), 4.75 (s, 2H), 3.79 (s, 3H), benzamide 3.42 (s, 3H).		1, 33
302	443	H ₃ C, CH ₃ H ₃ C, CH ₃ H ₃ C CH ₃ N ₃ C, CH ₃ N ₄ C, CH ₃ N ₅ C	<u> </u>	CH.	N-(2-Amino-phenyl)- 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.66 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.20 (dd, J = 6.6, 8.4 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.55 silanyloxy)-ethyl- $^{(1)}$ 6.83 (d, J = 7.0 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.44 (innethoxy- henyl)-aminol- $^{(2)}$ 7.07 (j = 5.7 Hz, 2H), 4.93 (s, 2H), 4.67 (s, 2H), 3.88 (t, J = 5.7 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.60 (t, J = 5.5 Hz), 0.96 (s, 9H), 0.06 (s, 6H).	6) 8 (ppm): 9.66 (s, 1H), (d, J = 7.9 Hz, 2H), 7.20 J = 6.6, 8.4 Hz, 1H), (d, J = 8.8 Hz, 1H), 6.65 (d, J = 2.6 Hz, 1H), 4.93 (s, 2H), 4.67 (s, 1.71 (s, 3H), 3.67 (s, 3H), H), 0.06 (s, 6H).	33
303	444	Meo OMe	СН	ᆼ	14 NMR (300 MHz, DMSO-ds) & (ppm)8 (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 ((dd, J = 7.0, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.44 (s, 1H), 6.19 ethyl)-aminol-(d, J = 8.8 Hz, 1H), 4.94 (s, 2H), 4.79 (m, 1H), 4.66 (s, 2H), 3.67 and 3.71 (2s and broading underneath, 8H), 3.55 (m, 2H).	- S	33, 23

EX.	Pg C	A	>	7	Name Characterization	Cohm
304	445	MeO Neo OMe	픙		nino-phenyl)- .5- oxy- amino)-	33
305	446		ᆼ	z	N-{2-Amino-phenyl}	m
306	447	F ₃ CO N'X	H H		N(2-Amino-phenyl)- ¹ H NMR (300 MHz, DMSO-d ₆) & (ppm); 9.37 (s, 1H), 4-{bis-(3-187.37 (m, 6H), 7.17 (d, J = 7.0 Hz, 1H), 6.99 (dd, J) 33 benzyl}-minol- 7.5 Hz, 1H), 4.94 (s, 4H), 4.86 (s, 2H).	33
307	448	H ₃ C, N NH Y, NH Y, NH	늉	끙	N-(2-Amino-phenyl)- 1 H NMR (300 MHz, DMSO-de) δ (ppm): 9.58 (s, 1H), 4-[(2-7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.56 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.44 (d, J = 8.4 Hz, benzamide	33
308	449	IZ ZI	5 :	퓽	N-(2-Amino-phenyl)	33

EX.	Cpd	W	>	7	Z Name Ct	Characterization	Schm
		TZ- O=			N-{2-Amino-phenyl}-	¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.60 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H),	
309	450	HS HS CH	끙	끙	trifluoromethylsulfa	7	33
		± + ±			methyl]-benzamide ====================================	methyl]-benzamide (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 7.9 Hz, 1H), 4.88 (bs, 2H), 4.72 (d, J = 6.2 Hz, 2H).	
					H	¹ H NMR (300 MHz, CD ₃ 0D) 8 (ppm): 8.67 (d, J = 1.8	
					N-(2-Amino-phenyl)- Hz	N-(2-Amino-phenyl)- Hz, 1H), 8.47 (dd, J = 1.3, 4.4 Hz, 1H), 8.08 (s, 1H),	
					4-{[2-{pyridin-3-8.(03 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H),	
310	451	N N N N N N N N N N N N N N N N N N N	<u>ح</u>	Ę	ylmethylsulfanyl)- 7.8		22
2	2	\ \z:\ \z:	5	5	1H-benzoimidazol- 7.3		ر د
		r			5-ylaminol-methyl}- 1	5-ylamino]-methyl}- 1.3, 8.4 Hz, 1H), 6.94 (dd, J = 1.3, 7.9 Hz, 1H), 6.77	
					benzamide (d,	, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.65 (d, J	
					11	= 1.8 Hz, 1H), 4.55 (s, 2H); 4.20 (bs, 2H); 3.36 (s, 2H).	
					N-72-Amino-ohenvil-	¹ H NMR (300 MHz, CD ₃ 0D) 8 (ppm): 8.60 (s, 1H),	
		+				8.36 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H),	
,		¥			ہے	7.87 (m, 1H); 7.47 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 6.6	
311	452	HO HO CH CH	프 당	ᆼ			33
					لہ	87 (d, J = 7.9 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.66	
		-				(s, 1H); 6.61 (d, J = 8.8 Hz, 1H), 4.87 (s, 2H); 4.45 (s,	
						2H); 4.3/ (s, 2H); 3.35 (s, 2H).	
		(N(2-Amino-5-	¹ H NMR (300 MHz, CDCI ₃) 8 (ppm): 8.21 (s, 1H); 7.90	
		»=(⟨			trifluoromethyl- (d,	, J = 8.4 Hz, 2H); 7.54 (m, 1H); 7.50 (d, J = 8.4 Hz,	•
312	453	HN			phenyl)-4-[(3,4-		22
1	?				dimethoxy- (d,		c C
		MeO F ₃ C			phenylamino)- · J =	J = 2.2, 8.8 Hz, 1H); 4.43 (s, 2H); 4.29 (s, 2H); 3.84	
		·			methyll-benzamide (s, 6H)	, 6H).	

EX.	Cpd	M	>	Z	Name Characterization	Schm
313	454	MBO H NH2			N(2-Amino-4,5-difluoro-phenyl)-4- (d, J = 7.9 Hz, 2H); 7.45 (d, J = 7.9 Hz, 2H); 7.85 (d, J = 7.9 Hz, 2H); 7.20 (dd, J = 3.9, 7.9 Hz, 1H); 6.76 (d, J = 8.8 Hz, 1H); 6.57 (dd, J = 3.9, 7.9 Hz, 1H); 6.32 (d, J = 2.6 Hz, 1H); 6.30 (d, J = 2.6 Hz, 1H); 6.40 (s, 2H); 3.82 (s, QH)	
314	455	IN O	동	CH CH	N-(2-Amino-phenyl)- ¹ / ₁ NMR (300 MHz, DMSO-d ₆) 8 (ppm); 9.60 (s, 1H); 4-[(2-oxo-2,3-7.93 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); dihydro- 7.16 (d, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.27 (m, 2H); 4.88 (bs, 2H); 4.34 (d, J = 6.2 benzamide	H);
315	456	Mehln S S S S S S S S S S S S S S S S S S S	끙	НЭ	phenyl)- lamino- ol-5- ethyl]-	= 7.9 Hz, HJ, 33
316	457	MeO H ₂ N MeO MeO			N-(2,6-Diamino-	88 , J 33
317	458	MeO NH X.	H	5	N-(2-Amino-phenyl)- 7.95 (d, J = 7.9 Hz, 2H); 7.73 (t, J = 5.7 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.47 (d, J = 7.9 Hz, 2H); 7.15 (d, J = 8.4 Hz, 1H); 7.47 (d, J = 7.9 Hz, 2H); 7.15 (d, J = 7.9 Hz, 1H); 6.97 (d, J = 7.5 Hz, 1H); 6.92 (bs, Z,3-dihydro-1H-1H); 6.86 (d, J = 8.4 Hz, 1H); 6.77 (d, J = 7.9 Hz, 1H); isoindol-5-ylaminol-6.59 (t, J = 7.5 Hz, 1H); 4.89 (bs, 2H); 4.54 (d, J = methyl}-benzamide 5.7 Hz, 2H); 3.65 (t, J = 5.3 Hz, 2H); 3.47 (t, J = 5.3 Hz, 2H); 3.47 (t, J = 5.3 Hz, 2H);	1); d, d, H);

Cpd		*	Υ	2	Name	Characterization	Schm
459 O O O O O O O O O O O O O O O O O O O			CH	동	N-(2-Amino-phenyl)-4-{(3-spiro[1',2']dioxolan e-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-ylamino)-methyl}-benzamide	N-(2-Amino-phenyl)- 14 NMR (300 MHz, DMSO-d ₆) & (ppm): 9.59 (s, 1H); 4-{(3- 7.92 (d, J = 8.3 Hz, 2H); 7.46 (d, J = 8.3 Hz, 2H); 5.15 (d, J = 7.5 Hz, 1H); 6.96 (t, J = 7.0 Hz, 1H); 6.78- 6.71 (m, 3H); 6.26.54 (m, 2H); 6.26 (t, J = 7.5 Hz, 1H); 4.87 (s, 2H); 4.36-4.32 (m, 4H); 4.23-4.19 (m, methyl)-benzamide	33
ب ^۲ ز ۱۳۳ کی ا	ێڒ <mark>×</mark>		СН	z		¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 2.5, 8.9 Hz, 1H), 7.58 (m, 1H); 7.51 (m, 1H); 7.15 (dd, J = 1.1, 7.7 Hz, 1H), 7.08 (m, 2H); 6.89 (dd, J = 1.4, 8.0 Hz, 1H), 6.76 (dt, J = 4.4, 7.7 Hz, 1H), 6.67 (d, J = 7.7 Hz, 2H), 6.60 (m, 2H); 4.87 (bs, 2H); 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H).	. 33
461 H ₃ C _N O NH C C C C C C C C C C C C C C C C C C	NH X		·	끙	N(2-Amino-phenyl)- 4{(1,3-dimethyl- 2,4-dioxo-1,2,3,4- tetrahydro- quinazolin-6- ylamino)-methyl)- benzamide	N-(2-Amino-phenyl)- 14 NMR (300 MHz, DMSO-d ₆) 8 (ppm): 9.59 (s, 1H); 2,4-dioxo-1,2,3,4 7.22 (d, J = 7.9 Hz, 1H); 7.16-7.09 (m, 3H); 6.96 (t, J tetrahydro-guinazolin-6- 2H); 4.87 (s, 2H); 4.42 (d, J = 5.3 Hz, 2H); 3.44 (s, benzamide	33
462 NH YH	NH NH	\circ	H	СН	N-(2-Amino-phenyl)- 4-[(6-methyl-6H- indolo[2,3- b]quinoxalin-9- ylamino)-methyl]- benzamide	N-{2-Amino-phenyl}- (4, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 7.55 (d, J = 7.9 Hz, 2H); 7.76 (t, J = 7.0 Hz, 1H); 7.55 (d, J = 7.9 Hz, 1H); 7.57 (d, J = 7.9 Hz, 2H); 7.54 (d, J = 8.8 Hz, 1H); 7.14 (d, J = 1.3 Hz, 1H); 7.22 (dd, J = 1.8, 8.8 Hz, 1H); 7.14 (d, J = 7.9 Hz, 1H); 6.95 (t, J = 7.5 Hz, 1H); 6.76 (t, J = 7.9 Hz, 1H); 6.57 (t, J = 7.5 Hz, 1H); 6.51 (bs, 1H); 4.86 (bs, 2H); 4.54 (d, J = 4.8 Hz, 2H); 3.85 (s, 3H).	33

EX.	Cpd	A	>	7	Name	Characterization	Schm
322	463	HO HO	Z	끙	M(2-Amino-phenyl)- 6-(1-hydroxy- cyclohexylethynyl)- nicotinamide	M(2-Amino-phenyl)- 6-(1-hydroxy- cyclohexylethynyl)- nicotinamide	14, 3
323	464	H ₃ C	z	H)	lenyl)- lyl-	LRMS calc: 335.42, found: 336.1 (MH)*	14, 3
324	465	HN NH	СН	끙	NK2-Amino-phenyl)- 4-[5-(indan-2- ylaminomethyl)- thiophen-2- ylmethyl]- benzamide	LRMS calc: 453.6, found: 454.2 (MH)*	21
325	466	NH N	G.	끙	NK2-Amino-phenyl)- 4-[5-(pyridin-2- ylaminomethyl)- thiophen-2- ylmethyl]- benzamide	LRMS calc: 414.52, found: 415 (MH)+	21
326	467	N N N N N N N N N N N N N N N N N N N	용	끙	N42-Amino-phenyl)- 4-[(5-bromo-thiazol- 2-ylamino)-methyl]- benzamide	LRMS calc: 403.3, found: 404 (MH)+	21
327	468	CH HN-N CH	픙	끙	N(2-Amino-phenyl)- 4-[(5-phenyl-1 H- pyrazol-3-ylamino)- methyl]-benzamide	LRMS calc: 483.45, found: 484.1 (MH)⁺	21

Fable 4c

				·
	Schm	33, 55	33, 55	33, 60
spunodwo	Characterization	¹ H NMR (DMSO-d ₆): 5 9.57 (brs, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.07 (t, J = 8.3 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.9 Hz, 1H), 6.21 (t, J = 6.1 Hz, 1H), 5.95 (s, 2H), 4.38 (d, J = 5.7 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H).	¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.9 (bs, 1H), 9.53 (s, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.08 (dd, J = 7.5, 7.5 Hz, 1H), 6.96 (d, J = 7.9, Hz, 1H), 6.88 (dd, J = 7.5, 7.5 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.38 (s, 1H), 6.05 (m, 2H), 4.36 (d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).	"H NMR: (Acetone-d ₆) δ (ppm): 9.09 (bs, 1H), 8.03 (d, 1=7.9Hz, 2H), 7.96 (d, 1=7.5 Hz, 1H), 7.65 (d, 1=7.9 Hz, 2H), 7.91 (d, 1=3.5 Hz, 1H), 7.51 (bs, 2H), 7.41 (d, 1)+4.([6-(2-morpholin-4-Hz, 2H), 7.61 (d, 1=3.5 Hz, 1H), 6.95 (d, 1=6.2 Hz, 1H), 6.95 (d, 1=6.2 Hz, 1H), 6.95 (d, 1=3.5 Hz, 1H), 4.85 (s, 2H), 4.20 (t, 1=5.7 Hz, 2.4 Hz, 4H), 2.87-2.81(m, 2H), 2.62-2.57 (m, 4H).
Characterization of Additional Compounds	Name	N42-Hydroxy-phenyl)-4 [(3,4,5-trimethoxy- phenylamino)-methyl]- benzamide	M2-hydroxy-phenyl}-4- [(3,4-Dimethoxy- phenylamino}-methyl]- benzamide	N(4-Amino-thiophen-3- yl)-4-{[6-(2-morpholin-4 yl-ethoxy}-benzothiazol 2-ylamino]-methyl}- benzamide
Characterization of	Compound	O NII	MeO H OH OH	S N2H N N N N N N N N N N N N N N N N N N
	Cpd	571	572	573
	Ex.	426	427	428

Schm	3, 60	36, 60		11	15, 33
Characterization	, 7.94 (d, J = 7.5 2-6.16 (m, 1H), = 5.7 Hz, 4H), 3.70	(DMSO) & (ppm):12.43 (bs, 1H), 9.59 (bs, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.32 (bs, 1H, SCH), 6.96 (bs, 1H, SCH), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 6.11(d, J = 3.7 Hz, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 3.76 (s, 3 H).LRMS:	2-{4-(4-Methoxy-7.63 (d, J=7.1 Hz, 1H), 7.53 (t, J= 4.2 Hz, 1H), 7.41 benzylamino}-phenyll- (dd, J=9.2, 1.5 Hz, 1H), 7.25 (d, J=8.3 Hz, 2H), 7.06 (d, cyclopropanecarboxyli J=7.1 Hz, 1H), 6.85 (d, J=8.3 Hz, 2H), 6.62-6.59 (m, c acid (2-amino-phenyl)-3H), 4.51 (d, J= 4.2 Hz, 2H), 3.78 (s, 3H), 2.77 (d, J=3.1 Hz, 1H), 2.45 (d, J=1.1 Hz, 1H), 1.22 (m, 1H), 1.05 (m, 1H).	M2-Amino-phenyl)-4(3- ¹ H NMR (DMSO-d ₆) & (ppm): 9.72 (brs, 1H), 8.23 (d, J cyano-6-methyl-pyridin- = 7.5 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2-yloxymethyl)- Hz, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.5 hz, 1H), 5.62 (brs, 2H), 4.97 (brs, 2H)	¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.63 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 5.3 Hz, 2H), 7.96 (m, 3H), 7.54 (d, J = 7.5Hz, 2H), 7.22 (dd, J = 5.3, 7.8 Hz, 2H), 7.01 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.64 (dd, J = 7.0, 7.9 Hz, 1H), 4.92 (s, 2H), 4.70 (d, J = 6.2 Hz, 2H), 3.98 (s, 3H).
Name	N(4-Amino-thiophen-3- yl)-4-[(3,4,5-trimethoxy- phenylamino)-methyl]- benzamide	N(4-Amino-thiophen-3- yl)-4-(5-methoxy-1 H- benzoimidazol-2- ylsulfanylmethyl)- benzamide	2-{4-(4-Methoxy-benzylamino}-phenyll-cyclopropanecarboxylicacid (2-amino-phenyl)-amide	M2-Amino-phenyl)-4(3- cyano-6-methy-pyridin- 2-yloxymethyl)- benzamide	M(2-Amino-phenyl)-4- I[4-(6-methoxy-pyridin- 3-yl)-pyrimidin-2- ylamino]-methyl}- benzamide
Compound	MeO H NH2	H ₃ C ^O H _{2N} H _{2N}	H ₃ C _N H	H ₃ C N N N N N N N N N N N N N N N N N N N	Meo NI
PdS	574	575	576	577	578
ᄶᆲ	429	430	431	432	433

Schm	s, 11H), 7.3 49 7.3 49	5 6.31 61 2 (d,	-	1), 3.0 2, 59 (t, 2H),
Characterization	¹ H NMR: (DMSO) δ (ppm): 11.98 (bs, 1H), 9.61 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.81 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 6.99 (dd, J = 7.3, 7.3 Hz, 1H), 4.88 (bs, 2H), 4.10, 21.5, 21.	¹ H NMR (DMSO) & (ppm): 9.56 (s, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 13.2, 8.35 Hz, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.39 (s, 1H), 6.31 (m, 2H), 5.75 (t, J = 6.15 Hz, 1H), 4.87 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.82 (d, J = 8.5 Hz, 3H).		¹ H NMR (DMSO) δ (ppm): 9.84 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.78 (m, 3H), 6.59 (t, J = 7.5 Hz, 1H), 5.71 (s, 2H), 4.94 (s, 1H), 4.65 (s, 2H), 3.76 (s, 3H).
Name	2-Acetylamino-5-[4-(2-amino-per)]-phenylcarbamoyl)-benzylj-thiophene-3-carboxamide	MC2-Amino-phenyl)-4- [(3-methyl-2- methylamino-3H- benzoimidazol-5- ylamino}-methyl]- benzamide		5-(5-Methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzofuran-2-carboxylic acid (2-amino-phenyl)amide
Compound	H ₂ C + C + C + C + C + C + C + C + C + C +	Men A A A A A A A A A A A A A A A A A A A		MeO - NH HN H ₂ N
Cpd	579	580		591
Ĕ.	434	435		438

Scheme 21

Example 122

Step 1: {2-[(3'-Formyl-biphenyl-4-carbonyl)-aminol-phenyl)-carbamic acid tert-butyl ester (185)

[0250] Following the procedure described in Example 15, step 1, but substituting 184 for 140, the title compound 185 was obtained in 74% yield. 1 H NMR (CDCl₃): δ 10.10 (s, 1H), 9.41(s, 1H), 8.13 (m, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.89 (m, 2H), 7.77 (m, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (m, 1H), 7.27-7.09 (m, 3H), 7.03 (s, 1H), 1.52 (s, 9H).

Step 2: N(2-Aminophenyl)-4-[3-(indan-2-ylaminomethyl)phenyl)]-benzamide (186)

[0251] To a stirred solution of biphenyl aldehyde (104 mg, 0.25 mmol) and 2-aminoindane (33.3 mg, 0.25 mmol) in dichloroethane (1mL) was added sodium triacetoxyborohydride (80 mg, 0.375 mmol) followed by a glacial acetic acid (15ul, 0.25 mmol), and then the mixture was stirred at room temperature for 3h. After a removal of the volatiles, the residue was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The combined organic layers were washed with water, dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired Boc-monoprotected product (112mg, 84% yield) as a white solid. ¹H NMR (CDCl₃): ±09.21 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.83 (m, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.65 (s, 1H), 7.54-7.38 (m, 3H), 7.28 (m, 7H), 6.82 (s, 1H), 3.95 (s, 2H), 3.74 (m, 1H), 3.22 (dd, J = 15.6, 6.9 Hz, 2H), 2.89 (dd, J = 15.6, 6.6 Hz, 2H), 1.53 (s, 9H).

[0252] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **186** was obtained in 98 % yield. 1 H NMR (20% CD₃OD in CDCl₃): δ 7.95 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (m, 1H), 7.54-6.79 (m, 11H), 3.95 (s, 2H), 3.66 (m, 1H), 3.16 (dd, J = 15.6, 6.9 Hz, 2H), 2.81 (dd, J = 15.6, 6.6 Hz, 2H).

Examples 123-126

[0253] Examples 123 to 126 (compounds 187 - 190) were prepared using the same procedure as described for compound 186 in Example 122 (scheme 21).

Scheme 22

Example 127

Step 1: {2-[4-(1-Amino-cyclohexylethynyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (191) [0254] A mixture of iodide 184 (438 mg, 1.0 mmol), Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol), triphenylphosphine (7.6 mg, 0.025 mmol), and 1-ethynylcyclohexylamine (185 mg, 1.5 mmol) was stirred at room temperature in THF (4 mL) containing triethylamine (0.56 mL, 4.0 mmol) for 20 min. To this Cul (3.8 mg, 0.02 mmol) was added and stirring continued for 2 h. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with water, and the organic layer was dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired product **191** (420 mg, 97% yield). ¹H NMR (CDCl₃): δ 9.36 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.25-6.85 (m, 3H), 2.10-1.30 (m. 10H), 1.51 (s, 9H). Step 2: N42-Aminophenyl)-4-[1-(4-methoxy-benzylamino)-cyclohexylethynyl]-benzamide (192) [0255] Following the procedure described in Example 122, step 2, but substituting panisaldehyde for 2-aminoindane, the title compound 192 was obtained in 74 % yield. ¹H NMR (CDCl₃): δ 8.44 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.23 (m, 1H), 7.05 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.78 (m, 2H), 3.97 (s, 2H), 3.76 (s, 3H), 2.10-1.30 (m. 10H).

Scheme 23

Example 133

Step 1: N{2-(t-Butyloxycarbonyl)-amino-phenyl]-4-(trimethylsilylethynyl)benzamide (197)

[0256] To a stirred solution of 184 (5.00 g, 11.41 mmol) in anhydrous THF (100 ml) under nitrogen at 0°C were added Pd(PPh₃)₂Cl₂ (240 mg, 0.34 mmol), Cul (130 mg, 0.69 mmol), and trimethylsilylacetylene (2.10 ml, 14.84 mmol), respectively. Then, anhydrous Et₃N (6.36 ml, 45.66 mmol) was added dropwise. The temperature was slowly warmed up to room temperature over 4 h. The reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 20/80 \rightarrow 50/50) to afford the title compound 197 (4.42 g, 10.83 mmol, 94% yield) as a yellow powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.26 (bs, 1H), AB system (δ _A = 7.91, δ _B = 7.55, J = 8.3 Hz, 4H), 7.85 (d, J = 7.9 Hz, 1H), 7.32-7.13 (m, 3H), 6.70 (bs, 1H), 1.53 (s, 9H), 0.28 (s, 9H).

Step 2: N(2-Amino-phenyl)-4-(trimethylsilylethynyl)benzamide (198)

[0257] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **198** (70 mg, 0.23 mmol) was obtained as a white solid with a major fraction composed of a mixture of **198** and **199**. 1 H NMR (300 MHz, acetone-d₆) δ (ppm): 9.20 (bs, 1H), AB system (δ_A = 8.07, δ_B = 7.62, J = 8.2 Hz, 4H), 7.32 (d, J = 7.6 Hz, 1H), 7.05 (td, J = 7.6, 1.2 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.3 Hz, 1H), 4.66 (bs, 2H), 0.30 (s, 9H). Step 3: N(2-Amino-phenyl)-4-ethynylbenzamide (**199**)

[0258] To a stirred solution at -20° C of a mixture of 198 and 199 in anhydrous THF (15 ml) under nitrogen was added a solution of TBAF (1 ml, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 18 h. Then, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 30/70) to afford the title compound 199 (215 mg, 0.91 mmol, 46% yield over 2 steps) as a pale yellow powder. ¹H NMR (300 MHz, acetone-d₆) δ (ppm): 9.19 (bs, 1H), AB system (δ _A = 8.08, δ _B = 7.66, J = 8.5 Hz, 4H), 7.33 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 4.67 (bs, 2H), 3.88 (s, 1H).

Example 134

Step 1: N[2-(t-Butyloxycarbonyl)-amino-phenyl]-4-ethynylbenzamide (200)

[0259] To a stirred solution at -20° C of a mixture of 199 (3.48 g, 8.53 mmol) in anhydrous THF (50 ml) under nitrogen was slowly added a solution of TBAF (9.4 ml, 9.38 mmol, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 4 h. Then, the reaction mixture was concentrated, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: $25/75 \rightarrow 30/70$) to afford the title compound 200 (2.53 g, 7.53 mmol, 88% yield) as a pale yellow foam. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.31 (bs, 1H), AB system ($\delta_A = 7.94$, $\delta_B = 7.59$, J = 8.5 Hz, 4H), 7.83 (d, J = 7.6 Hz, 1H), 7.30-7.10 (m, 3H), 6.75 (bs, 1H), 3.23 (s, 1H), 1.53 (s, 9H).

Step 2: N(2-amino-phenyl)-4-[3-(4-chlorophenyl)-3-morpholin-4-yl-1-propyn-1-yl]-benzamide (201)

To a stirred solution at room temperature of **200** (200 mg, 0.60 mmol) in anhydrous 1,4-dioxane (5 ml) under nitrogen were added 4-chlorobenzaldehyde (100 mg, 0.71 mmol), morpholine (60 μ l, 0.68 mmol), and Cul (6 mg, 0.03 mmol), respectively. The reaction mixture was bubbled with nitrogen for 5 min and warmed up to 105°C. After 18 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the desired compound (193 mg, 0.35 mmol, 59% yield) as a pale yellow foam. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.40 (bs, 1H), AB system (δ_A = 7.96, δ_B = 7.36, J = 8.5 Hz, 4H), 7.79 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 8.4 Hz, 4H), 7.25-7.10 (m, 3H), 6.91 (s, 1H), 4.80 (s, 1H), 3.82-3.68 (m, 4H), 2.69-2.58 (m, 4H), 1.53 (s, 9H).

[O260] Following the procedure described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **201** was obtained in 67 % yield. ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.80 (bs, 1H), AB system (δ_A = 8.06, δ_B = 7.71, J = 8.1 Hz, 4H), AB system (δ_A = 7.65, δ_B = 7.52, J = 8.3 Hz, 4H), 7.20 (d, J = 7.9 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.64 (t, J = 7.5 Hz, 1H), 5.10 (s, 1H), 4.97 (bs, 2H), 3.72-3.58 (m, 4H), 2.67-2.46 (m, 4H).

Scheme 24 H₂N CO₂Me i-Pr₂NEt THF reflux 203 1. NH₃ 2. LiOH.H₂O 3. 1,2-phenylene-diamine, BOP

Example 135 204

Example 135

Step 1: Methyl 4-(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-benzoic ester (203)

[0261] To a stirred solution at room temperature of 202 (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added iPr₂NEt (1.86 ml, 10.66 mmol) and methyl 4-aminobenzoate (1.29 g, 8.53 mmol) or ArNH₂ (1.2 equiv), respectively. The reaction mixture was then refluxed for 24 h. After cooling, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 2/98 \rightarrow 5/95) to afford the title compound 203 (1.70 g, 4.30 mmol, 60% yield) as a beige powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 2 AB system (δ _A = 8.03, δ _{A'} = 8.00, δ _B = 7.70, δ _{B'} = 7.61, J_{AB} = J_{AB'} = 8.8 Hz, 4H), 7.43 and 7.31 (2 bs, 1H), 7.29-7.19 (m, 4H), 5.84 and 5.78 (2 d, J = 7.2 and 7.7 Hz, 1H), 4.98-4.77 (2 m, 1H), 3.91 and 3.90 (2 s, 3H), 3.41 (dd, J = 16.1, 7.0 Hz, 2H), 2.94 and 2.89 (2 dd, J = 15.9, 4.9 Hz, 2H).

Step 2: 4-[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide (204) [0262] The title compound 204 was obtained from 203 in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. 1 H NMR (300 MHz, acetone-d₆) δ (ppm): mixture of rotamers, 8.98 (m,1H), 8.49 and 8.28 (2m, 1H), 8.10-7.92 (m, 4H), 7.35-7.14 (m, 5H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 6.6, 1.3 Hz, 1H), 6.71 (td, J = 7.6, 1.3 Hz, 1H), 6.57 and 6.42 (2m, 1H), 6.04 and 5.86 (2m, 2H), 4.92-4.76 (m, 1H), 4.70-4.58 (m, 1H), 3.44-3.26 (m, 2H), 3.08-2.92 (m, 2H). HRMS (calc.): 452.2073, (found): 452.2062.

Scheme 25

Example 136

Step 1: Methyl 4-((4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yloxy)-methyl]-benzoic ester (206)

[0263] To a stirred solution at 0°C of **205** (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*Pr₂NEt (1.86 ml, 10.66 mmol) and methyl 4-(hydroxymethyl)benzoate (1.30 g, 7.82 mmol). After few minutes, NaH (95%, 186 mg, 7.11 mmol) was added portionwise. Then, the reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with *sat.* NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 2/98) to afford the title compound **206** (2.00 g, 4.88 mmol, 69% yield) as a colorless sticky foam. ¹H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 2 AB system (δ _A = 8.06, δ _A = 8.03, δ _B = 7.52, δ _{B'} = 7.46, J_{AB} = J_{AB'} = 8.5 Hz, 4H), 7.26-7.17 (m, 4H), 5.94 and 5.85 (2 bd, J = 7.8 Hz, 1H), 5.48 and 5.39 (2 s, 2H), 4.92-4.76 (2 m, 1H), 3.94 and 3.92 (2 s, 3H), 3.39 and 3.33 (2 dd, J = 16.0, 7.0 Hz, 2H), 2.89 and 2.84 (2 dd, J = 16.0, 4.9 Hz, 2H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yloxy]-methyl}-N-(2-amino-phenyl)-benzamide (207)

[0264] The title compound 207 was obtained from 206 in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. ¹H NMR (300 MHz, acetone- $d_6 + \Box$ DMSO- d_6) δ (ppm): 9.49 (m,

1H), 8.12-8.03 (m, 2H), 7.60 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 7.1 Hz, 1H), 7.28-7.13 (m, 4H), 7.07-6.94 (m, 2H), 6.90 (dd, J = 7.3, 1.4 Hz, 1H), 6.70 (td, J = 7.3, 1.1 Hz, 1H), 6.44 (bs, 1H), 6.25 (bs, 1H), 5.47 and 5.41 (2s, 2H), 4.87-4.68 (m, 3H), 3.35-3.20 (m, 2H), 3.02-2.88 (m, 2H). HRMS (calc.): 467.2070, (found): 467.2063.

Scheme 26

Example 210

Methyl 4-[(4-chloro-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (208)

[0265] The title compound **208** was obtained from **2** following the same procedure as in Example 1, pathway B steps 2 (R^1R^2NH = phenethylamine).

Step 1: Methyl 4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (209)

[0266] To a degazed solution of 208 (300 mg, 0.75 mmol) in MeOH (35 mL) was added 10% Pd/C (24 mg, 0.023 mmol). The reaction mixture was stirred under a 1 atm pressure of H₂ at room temperature for 20 h then it was purged with N₂. The palladium was removed by filtration through celite and the reaction mixture was concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 4/96) to afford the title compound 209 (135 mg, 0.37 mmol, 50% yield). 1 H NMR (300 MHz, CDCl₃) δ (ppm): 8.08 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.50-7.15 (m, 6H), 4.85-4.65 (m, 2H), 3.98 (s, 3H), 3.82-3.62 (m, 2H), 3.05-2.85 (m, 2H).

Step 2: N(2-Amino-phenyl)-4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide (210)

[0267] The title compound 210 was obtained from 209 in 2 steps following the same procedure as in Example 1, steps 4 and 5. 1 H NMR: (300 MHz, acetone-d₆) δ (ppm): 9.03 (s, 1H), 8.17-7.87 (m, 3H), 7.49 (dd, J = 19.2, 8.2 Hz, 2H), 7.32-7.03 (m, 6H), 6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-6.30 (m, 2H), 4.72 (t, J = 6.3 Hz, 1H), 4.65-4.56 (m, 1H), 3.67-3.51 (m, 2H), 2.95-2.80 (m, 2H).

Scheme 27

Example 138

Step 1: Methyl 4-[(4,6-dimethoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (211)

[0268] In a 75ml sealed flask, a stirred suspension of 2-chloro-4,6-dimethoxy-1,3,5-triazine (540 mg, 3.08 mmol), methyl 4-(aminomethyl)benzoate.HCl 2 (689 mg, 3.42 mmol), iPr₂NEt (1.49 ml, 8.54 mmol) in anhydrous THF (30 ml) was warmed at 80°C for 5 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 10/90→30/70) to afford the title compound 211 (870 mg, 2.86 mmol, 93% yield) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): AB

system ($\delta_A = 8.01$, $\delta_B = 7.39$, $J_{AB} = 8.5$ Hz, 4H), 6.08-6.00 (m, 1H), 4.73 (d, J = 6.3 Hz, 2H), 3.95 (s, 6H), 3.92 (s, 3H).

[0269] The title compound 212 was obtained from 211 in 2 steps following the same procedure as Example 1, steps 4 and 5. 1 H NMR (300 MHz, acetone-d₆ + Σ DMSO-d₆) δ (ppm): 9.58 (bs, 1H), 8.27 (t, J = 6.3 Hz, 1H), AB system (δ_A = 8.04, δ_B = 7.53, J_{AB} = 8.4 Hz, 4H), 7.31 (d, J = 6.9 Hz, 1H),), 7.02 (td, J = 7.6, 1.6 Hz, 1H), 6.88 (dd, J = 7.9, 1.4 Hz, 1H), 6.68 (td, J = 7.6, 1.4 Hz, 1H), 4.86-4.78 (m, 2H), 4.69 (d, J = 6.3 Hz, 2H),), 3.90 and 3.89 (2s, 6H). HRMS (calc.): 380.1597, (found): 380.1601.

Step 2: N(2-Amino-phenyl)-4-[(4,6-dimethoxy-[1,3,5]-triazin-2-yl-amino)-methyl]-benzamide (212)

Scheme 28

Example 139

Step 1: 4-[(6-(2-Indanyl-amino)-4-methoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (213)

[0270] To a stirred solution at room temperature of **5** (300 mg, 0.73 mmol) in a mixture of MeOH/THF (10 ml/5 ml) was added an aqueous solution of KOH (10%, 5 ml). After 3 days, the reaction mixture was concentrated on the rotavap, diluted in water and acidified with 1N HCl until pH 5-6 in order to get a white precipitate. After 15 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **213** (282 mg, 0.72 mmol, 98% yield) as a white solid. MS: m/z = 392.1 [MH]⁺.

Step 2: N{2-amino-phenyl}-4-{[6-{2-indanyl-amino}-4-methoxy-[1,3,5]-triazin-2-yl-amino}-methyl}-benzamide (214)

[0271] The title compound 214 was obtained from 213 in one step following the same procedure as Example 1, step 5. 1 H NMR (300 MHz, acetone-d₆ + [] DMSO-d₆) δ (ppm): mixture of rotamers, 9.69-9.53 (m, 1H), AB system (δ_A = 8.04, δ_B = 7.52, J_{AB} = 7.8 Hz, 4H), 7.80-7.60 (m, 1H), 7.45-7.10 (m, 6H), 7.01 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 4.92-4.60 (m, 5H), 3.90-3.78 (m, 3H), 3.35-3.22 (m, 2H), 3.02-2.83 (m, 2H). HRMS (calc.): 481.2226, (found): 481.2231.

Scheme 29

Example 29

Step 1: Methyl 4-[(4,6-dichloro-[1,3,5]triazin-2-yl-N-methyl-amino)-methyl]-benzoic ester (216)

[0272] To a stirred suspension at room temperature of NaH (95%, 81 mg, 3.19 mmol) in anhydrous THF (10 ml) under nitrogen were successively added a solution of 3 (500 mg, 1.60 mmol) in anhydrous THF (10 ml) and MeI (298 μ I, 4.79 mmol). After 16 h, the reaction mixture was poured into a saturated aqueous solution of NH₄CI, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄CI, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel

(AcOEt/hexane: $10/90 \rightarrow 20/80$) to afford the title compound **215** (200 mg, 0.61 mmol, 38% yield) as a white crystalline solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): AB system ($\delta_A = 8.04$, $\delta_B = 7.31$, $J_{AB} = 8.2$ Hz, 4H), 4.93 (s, 2H), 3.93 (s, 3H), 3.18 (s, 3H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-N-methyl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (216)

[0273] The title compound 216 from 215 in 4 steps was obtained following the same procedure as Example 1, Pathway B steps 2-5. 1 H NMR (300 MHz, acetone-d₆) δ (ppm): 9.11 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.43 (bs, 2H), 7.33 (d, J = 7.7 Hz, 1H),), 7.28-7.09 (m, 4H), 7.04 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.5, 1.3 Hz, 1H), 6.25-6.05 (m, 1H), 5.82 and 5.64 (2bs, 2H), 5.00-4.56 (m, 5H), 3.42-2.76 (m, 7H). HRMS (calc.): 480.2386, (found): 480.2377.

Scheme 30

Example 141:

Example 141 218 : $R^1 = Me$, $R^2R^3N = 2$ -indanyl-amino

Step 1: Methyl 4-[(4-chloro-6-methyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (217)

[0274] To a stirred solution at -30° C of cyanuric chloride **1** (2.00 g, 10.85 mmol) in anhydrous THF (100 ml) under nitrogen was slowly added a solution of MeMgBr (17 ml, 23.86 mmol, 1.4 M in anhydrous THF/toluene). After 1 h, the reaction mixture was allowed to warm to room temperature over 3 h. Then, methyl 4-(aminomethyl)benzoate.HCl **2** (2.08 g, 10.30 mmol) and i-Pr₂NEt (3.78 ml,

21.69 mmol) were added, respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: $10/90 \rightarrow 15/85$) to afford the title compound **217** (780 mg, 2.67 mmol, 25% yield) as a yellow powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 2 AB system (δ _A = 8.03, δ _{A'} = 8.02, δ _B = 7.39, δ _{B'} = 7.38, J = 8.5 Hz, 4H), 6.28-6.08 (2 m, 1H), 4.76 and 4.74 (2d, J = 6.3 Hz, 2H), 3.92 (s, 3H), 2.46 and 2.42 (2s, 3H).

Step 2: N-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-methyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide (218)

[0275] The title compound 218 was obtained from 217 in 3 steps following the same procedure as Example 1, steps 3-5. 1 H NMR (300 MHz, acetone-d₆ + Σ DMSO-d₆) δ (ppm): mixture of rotamers, 9.62-9.50 (m, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.68-7.37 (m, 3H), 7.33 (d, J = 7.7 Hz, 1H), 7.28-7.07 (m, 5H), 7.02 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 4.92-4.60 (m, 5H), 3.35-3.10 (m, 2H), 3.02-2.82 (m, 2H), 2.25-2.12 (m, 3H).

Scheme 31

Example 142

Step 1: (2-[4-[2-[4-,6-Diamino-[1,3,5]triazin-2-yl]-vinyl]-benzoylamino}-phenyl)-carbamic tert-butyl ester (219)

[0276] To a degazed solution of 184 (40 mg, 0.091 mmol) and 2-vinyl-4,6-diamino-1,3,5-triazine (11 mg, 0.083 mmol) in dry DMF (1 mL) was added tri-o-tolylphosphine (POT) (1.5 mg, 0.005 mmol) followed by $\rm Et_3N$ (46 $\rm \mu L$, 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.0025 mmol). The solution was heated at 100°C for 16h. Then, DMF was removed under reduced

pressure. The reaction mixture was partitioned between AcOEt and a solution of sat. NH₄Cl. After separation, the organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 5/95) to afford the title compound **219** (25 mg, 0.056 mmol, 67% yield). ¹H NMR (300 MHz, Acetone-d₆) δ (ppm): 8.27 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 15.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.76-7.69 (m, 1H), 7.62-7.55 (m, 1H), 7.26-7.15 (m, 2H), 6.90 (d, J = 15.9 Hz), 6.21 (s, 4H), 1.50 (s, 9H).

Step 2: N(2-Amino-phenyl)-4-[2-(4,6-diamino-[1,3,5]triazin-2-yl)-vinyl]-benzamide (220)

[0277] To a stirred solution at room temperature of 219 (25 mg, 0.056 mmol) in CH_2CI_2 (1.5 mL) was added TFA (0.3 mL, 4.3 mmol). After 30 min, a solution of sat. NaHCO₃ was slowly added until pH 8 is reached, CH_2CI_2 was removed under reduced pressure, AcOEt was added, and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/CH₂CI₂: 10/90) to afford the title compound 220 (19 mg, 0.054 mmol, 98% yield). ¹H NMR: (300 MHz, acetone-d₆) δ (ppm): 8.33, 8.13 (2d, J = 7.5 Hz, 1H), 8.22 (d, J = 15.9 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.38-6.96 (m, 2H), 7.03 (d, J = 15.9 Hz, 1H), 6.94-6.62 (m, 2H).

Scheme 32

Example 143a

Step 1: 2-Amino-4-chloro-6-piperidin-1-yl-[1,3,5]triazin (221)

[0278] Ammonia was bubbled for 5 min in a solution of 2,4-dichloro-6-piperidin-1-yl-[1,3,5]triazine (500 mg, 2.15 mmol) in dry 1,4-dioxane (20 mL). The solution was heated at 70° C for 16h in a sealed tube. The reaction mixture was allowed to cool to room temperature, and partitioned between AcOEt and a solution of sat. NH₄Cl. After separation, the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford the title compound **221** (453 mg, 2.12 mmol, 98% yield). LRMS: [MH]⁻⁺ = 214.1.

Step 2: 2-Amino 4-piperidin-1-yl-6-vinyl-[1,3,5]triazin (222)

[0279] To a solution of **221** (358 mg, 1.68 mmol) in dry toluene (7 mL) was added tributyl(vinyl)tin (514 μL, 1.76 mmol) followed by Pd(PPh₃)₄ (97 mg, 0.084 mmol) and the reaction mixture was heated at 100°C for 16h in a sealed tube. Then, the reaction mixture was allowed to cool to room temperature, concentrated, and purified directly by flash chromatography on silica gel (AcOEt/hexane: $10/90 \rightarrow 30/70$) to afford the title compound **222** (containing tributyltin chloride). Steps 3: N(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-vinyl]-benzamide (**223**) [**0280**] The title compound **223** was obtained from **222** in 2 steps following the same procedure as in scheme 31, steps 1 and 2. ¹H NMR: (300 MHz, DMSO-d₆) δ (ppm): 9.69 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 16.0 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.04-6.92 (m, 1H), 6.91 (d, J = 16 Hz, 1H), 6.85-6.68 (m, 3H), 6.60 (t, J = 7.2 Hz, 1H), 4.93 (s, 2H), 3.77 (s, 4H), 1.63 (s, 2H), 1.52 (s, 4H).

Example 143b

Step 4: N(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yH1,3,5]triazin-2-yl)-ethyl]-benzamide (224) [0281] To a solution of 223 (18 mg, 0.043 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 0.021 mmol). The reaction mixture was shaked under a pressure of H₂ (40 psi) at room temperature for 16 h using an hydrogenation apparatus. Then, the reaction mixture was purged with N₂, filtered through celite, and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: $2/98\rightarrow4/96$) to afford the title compound 224 (10 mg, 0.024 mmol, 56% yield). ¹H NMR (300 MHz, CDCl₃-CD₃OD) δ (ppm): 7.82 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 6.89-6.79 (m, 2H), 7.80-6.90 (m, 1H), 3.76 (s, 4H), 3.13 (t, J = 8.1 Hz, 2H), 2.88 (t, J = 8.1 Hz, 2H), 1.90-1.40 (m, 10H).

BOP, Et₃N

Example 144

1,2-phenylenediamine

227

Step 1: 2-Amino-benzothiazol-6-ol (225):

228 Example 144

[O282] A suspension of 2-amino-6-methoxybenzothiazole (5.00 g, 27.8 mmol) in dichloromethane (70 mL) was cooled to 0°C under nitrogen and boron tribromide (3.93 mL, 41.6 mmol) was added dropwise. The light yellow mixture was stirred for 3 h, allowing to warm-up slowly from 0°C to 10°C. The reaction was slowly quenched by dropwise addition of methanol and tafter stirring overnight at room temperature, the white solid was collected by filtration (6.04 g, 88% yield). This hydrobromic salt was dissolved in water, washed with ethyl acetate, and neutralized with a saturated aqueous solution of NaHCO₃. The resulting crystals were collected by filtration and dried in the oven at 135°C for 1h to afford the title compound 225 as colorless crystals (3.63 g, 79% yield). ¹H NMR: (CD₃OD) δ (ppm): 7.27 (d, J=8.8 Hz, 1H), 7.08 (d, J=2.2 Hz, 1H), 6.80 (dd, J=8.4, 2.2 Hz, 1H).

[O283] To a solution of benzothiazole 225 (3.62 g, 21.8 mmol) in THF at room temperature under nitrogen, were successively added 4-(2-hydroxyethyl)morpholine (3.17 mL, 26.1 mmol), triphenylphosphine (7.43 g, 28.3 mmol) followed by a dropwise addition of diethyl azodicarboxylate (4.46 mL, 28.3 mmol). The solution was stirred for 3.5 h and THF was partially removed *in vacuo*. The mixture was partitioned between ethyl acetate and H₂O. The combined organic layers were extracted with 1N HCl. The combined acidic extracts were neutralized using a saturated aqueous solution of NaHCO₃ and the precipitate was dissolved with ethyl acetate. These combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The filtrate was concentrated to afford the title compound 226 (5.83 g, 96% yield) as a light yellow oil. ¹H NMR: (Acetone-d₆) δ

(ppm): 7.37 (d, J=8.8 Hz, 1H), 7.34 (d, J=2.6 Hz, 1H), 6.94 (dd, J=8.8, 2.6 Hz, 1H), 6.60 (bs, 2H), 4.19 (t, J=6.2 Hz, 2H), 3.70-3.67 (m, 4H), 2.90 (s, 2H), 2.81 (t, J=6.2 Hz, 2H), 2.62-2.58 (m, 4H). Step 3: 4-{[6-(2-Morpholin-4-yl-ethoxy}-benzothiazol-2-ylaminol-methyl}-benzoic acid methyl ester (227):

[0284] To a round-bottom flask containing benzothiazole 226 (5.80 g, 20.8 mmol) was added methyl 4-formylbenzoate (5.11 g, 31.1 mmol), followed by THF (8 mL), dibutyltin dichloride (315 mg, 1.04 mmol) and dropwise addition of phenylsilane (3.24 mL, 31.1 mmol). The resulting mixture was stirred overnight at room temperature under nitrogen. The mixture was diluted in ethyl acetate and filtered. The filtrate was partitioned between ethyl acetate and water and the combined organic layers were washed with 1N HCl. The combined acidic layers were neutralized using a saturated aqueous solution of NaHCO₃ and the precipitate was extracted with ethyl aceate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The resulting crude was purified by flash chromatography using MeOH/CHCl₃ (10:90) to afford 227 (3.69 g, 42% yield). ¹H NMR: (Acetone-d₆) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H). Step 4: N{2-Amino-phenyl}-4-{[6-{2-morpholin-4-yl-ethoxy}-benzothiazol-2-ylamino]-methyl}-benzamide (228):

[0285] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 228 was obtained (958 mg, 46%) as a colorless solid. 1 H NMR: (CD₃OD) δ (ppm): 8.04 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.8 Hz, 1H), 7.31 (d, J=2.5 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 6.97 (dd, J=8.8, 2.5 Hz, 2H), 6.84 (t, J=7.4 Hz, 1H), 4.78 (s, 2H), 4.21 (t, J=5.2 Hz, 2H), 3.81-3.77 (m, 4H), 2.87 (t, J=5.5, 2H), 2.69-3.66 (m, 4H).

Scheme 34

Example 145

Step 1: 4-[(5-Bromo-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (229):

[**0286**] Following the procedure described in Example 144, step 3, but substituting the 2-amino-6-bromobenzothiazole for **226**, the title compound **229** was obtained in 56% yield. 1 H NMR: (DMSO-d₆) δ (ppm): 8.78 (t, J= 5.9 Hz, 1H), 8.01 (d, J= 8.2 Hz, 2H), 7.99 (s, 1H), 7.56 (d, J= 8.2 Hz, 2H), 7.43-7.34 (m, 2H), 4.74 (d, J= 5.9 Hz, 2H), 3.90 (s, 3H).

Step 2: 4-([5-(3,4,5-Trimethoxy-phenyl)-benzothiazol-2-ylamino]-methyl)-benzoic acid methyl ester (230):

[0287] Following the procedure described in Example 15, step 1, but substituting 229 for 140, the title compound 230 was obtained in 44%yield as colorless crystals. 1 H NMR: (DMSO-d₆) δ (ppm): 8.73 (t, J=5.7 Hz, 1H), 8.11 (d, J=1.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H), 7.63-7.57 (m, 3H), 7.48 (d, J=8.4 Hz, 1H), 6.97 (s, 2H), 4.77 (d, J=5.7 Hz, 2H), 3.92 (m, 6H), 3.90 (s, 3H), 3.74 (s, 3H). Step 3: N{2-Amino-phenyl}-4-{[5-{3,4,5-trimethoxy-phenyl}-benzothiazol-2-ylamino]-methyl}-benzamide (231):

[0288] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **231** was obtained in 69% yield. 1 H NMR: (Acetone-d₆) δ (ppm): 8.31 (d, J=7.9 Hz, 2H), 8.20 (d, J=7.5 Hz, 1H), 8.13 (s, 1H), 7.73-7.58 (m, 3H), 7.63 (d, J=7.5 Hz, 2H), 7.48-7.43 (m, 2H), 7.05 (s, 2H), 4.98 (s, 2H), 4.00 (s, 6H), 3.84 (s, 3H).

Scheme 35

Example 146

Step 1: 4-[(6-Methoxy-benzothiazol-2-ylamino)-methyll-benzoic acid methyl ester (232):

[0289] To a solution of 2-amino-6-methoxybenzothiazole (2.00 g, 11.1 mmol) in a mixture of dichloroethane (20 mL) and THF (20 mL), were successively added methyl 4-formylbenzoate (1.82 g, 11.1 mmol), sodium triacetoxyborohydride (3.53 g, 16.7 mmol) and acetic acid (1.27 mL, 22.2 mmol). The mixture was stirred over 2 days and was quenched by adding aqueous saturated solution of NaHCO₃. The mixture was poured in a separating funnel containing water and was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc/ hexane (20:80 to 30:70) to afford the title compound 232 (1.85g, 51% yield). ¹H NMR: (Acetone-d₆) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J= 8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J= 8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H). Step 2: N42-Amino-phenyl)-4-[(6-methoxy-benzothiazol-2-ylamino)-methyl]-benzamide(233):

[0290] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **233** was obtained in 19% yield as a light beige solid. 1 H NMR: (DMSO-d₆) δ (ppm): 9.68 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.00 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.39 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.21 (d, J=6.6 Hz, 1H), 7.05 (t, J=6.3 Hz, 1H), 7.00 (d, J=1.4 Hz, 1H), 6.88 (dd, J=8.8, 2.7 Hz, 1H), 6.86 (dd, J=8.0, 1.4 Hz, 1H), 6.65 (td, J=7.4, 1.4 Hz, 1H), 4.95 (s, 2H), 4.70 (d, J=5.8 Hz, 2H), 3.79 (s, 3H).

Example 147

Step 1: 4-(6-Methoxy-1H-benzoimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester hydrobromide (234):

[0291] To a solution of methyl 4-(bromomethyl)benzoate (2.51g, 11.0 mmol) in DMF (50 mL) was added 5-methoxy-2-benzimidazolethiol (1.98g, 11.0 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated *in vacuo*. The residue was suspended in ethyl acetate and the hydrobromide salt was collected by filtration to afford the title compound **234** (4.10g, 91% yield) as a colorless solid. 1 H NMR: (DMSO-d₆) δ (ppm): 7.90 (d, J= 8.2 Hz, 2H), 7.55 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 1H), 7.03 (s,1H), 6.94 (d, J= 8.2 Hz,1H), 4.65 (s,2H), 3.82 (s,3H), 3.79 (s, 3H).

Step 2:: 4-[6-(2-Morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (235):

[0292] Following the procedure described in Example 144, step 1, 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound 235 was obtained in 37% yield. 1 H NMR: (CDCl₃) δ (ppm): 8.04-8.00 (m, 2H), 7.77-7.72 (m, 1H), 7.69-7.59 (m, 1H), 7.56-7.49 (m, 2H), 6.96-6.90 (m, 1H), 4.68 (s, 2H), 4.31-4.16 (m, 4H), 3.97 (s, 3H), 3.98-3.91 (m, 2H), 3.82-3.72 (m, 2H), 2.75-2.47 (m, 4H).

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyll-benzamide (236):

[0293] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **236** was obtained in 11% yield. 1 H NMR: (CD₃OD) δ (ppm): 7.89 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 2H), 7.28 (d, J= 8.5 Hz, 1H), 7.19-7.06 (m, 3H), 6.93-6.79 (m, 3H), 4.55 (s, 2H), 4.18 (t, J= 6.3 Hz, 2H), 3.65-3.62 (m, 4H), 2.51 (t, J= 6.6 Hz, 2H), 2.46-2.42 (m, 4H).

Scheme 37

Example 148

Step 1: 4-Morpholin-4-yl-benzoic acid methyl ester (237):

[0294] A flame-dried pressure vessel was charged with cesium carbonate (912 mg, 2.80 mmol) and toluene (8 mL) and the flasked was purged with nitrogen. Palladium acetate (9.0 mg, 0.004 mmol) and *rac*-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (37 mg, 0.06 mmol). The mixture was degassed and heated at 100°C for 18 h. It was allowed to cool to room temperature and was filtered through celite, rinsed with ethyl acetate and partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo* to afford the title compound **237** (443 mg, 100% yield). ¹H NMR: (CDCl₃) 8 (ppm):8.02 (d, J=9.2 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 3.95 (s, 4H), 3.92 (s, 3H), 3.38-3.35 (m, 4H). Step 2: N42-Amino-phenyl)-4-morpholin-4-yl-benzamide (**238**):

[0295] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **238** was obtained in 33 % yield. 1 H NMR: (DMSO-d₆) δ (ppm): 7.20 (d, J= 7.9 Hz, 1H), 7.07 (d, J= 8.8 Hz, 2H), 7.01 (t, J= 7.0 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.65 (t, J= 7.5 Hz, 1H), 4.90 (s, 2H), 3.81-3.79 (m, 4H), 3.32-3.28 (m, 4H).

Scheme 38

Example 149

Step 1: 3-Methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (239)

[0296] To a solution of pyridin-4-ylamine (1.0 g, 11.0 mmol) and 3,3-Bis-methylsulfanyl-acrylonitrile (2.05 g, 12.6 mmol) in DMF at room temperature, was added powdered 4A molecular sieves. The mixture was stirred for 1 hr. Subsequently the mixture was cooled to 0 °C, 60% NaH dispersion in oil (0.92 g, 23.0 mmol) was added portionwise over 1 hr. and it was stirred at 0 °C for an additional 2 hrs. The cold bath was removed and the mixture was stirred at room temperature for 20 hrs. DMF was removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 25% MeOH/EtOAc) to afford the desired product as an off-white solid (1.9 g, 89%). Step 2: N42-Amino-phenyl)-4-{[2-cyano-1-(pyridin-4-ylamino)-vinylamino]-methyl}-benzamide (240)

[0297] To a mixture of 3-methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (0.2 g, 1.0 mmol), 4-aminomethyl-benzoic acid (0.173 g, 1.14 mmol), DMAP (1 mg) and Et₃N (0.14 ml, 1.0 mmol) was added dry pyridine (0.5 ml). The resulting stirring mixture was heated to 55 °C for 4.5 hrs., additional Et₃N (0.14 ml) was added and mixture was heated from 75 °C to 90 °C over a period of ~30 hrs. When the reaction was complete, pyridine was partially removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 20% MeOH/EtOAc) to afford the desired product as an off-white solid (130 mg, 44%).

[0298] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for **6**, the title compound **240** was obtained in 33 % yield. 1 H NMR: 1 H NMR: (300 MHz, DMSO-d₆) δ (ppm): 9.69 (br, 2H), 8.48 (br, 3H), 8.03 (d, J = 7.9 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.29 (br, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.03 (t, J= 7.0 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 4.96 (br, 2H), 4.62 (d, J = 5.7 Hz, 2H).

Scheme 39

Example 150

· Step 1: 4-[(2-Chloro-9H-purin-6-ylamino)-methyl]-benzoic acid methyl ester (241)

[0299] A suspension of 2,6-dichloro-9*H*-purine (1 g, 5.29 mmol), 4-aminomethyl-benzoic acid methyl ester hydrochloride (1.2 equiv., 1.28 g) and NaHCO₃ (2.1 equiv., 935 mg) in water was heated at 100°C. The homogeneous solution thus formed was refluxed 30 min. The resulting white precipitate was filtered, washed with cold water and dried under vacuum giving the title compound 241 (1 g, 3.14 mmol, 60%). LRMS calc:317.7, found: 318.3 (MH)⁺.

Step 2: 4-{[2-Chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylaminol-methyl]-benzoic acid methyl ester (242)

[0300] Following the procedure described in Example 144, step 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound 242 was obtained in 41% yield. Step 3: N(2-Amino-phenyl)-4-{[2-chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylamino]-methyl}-benzamide (243):

[0301] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 243 was obtained in 85% yield. 1 H NMR (CDCl₃) δ (ppm): 9.64 (s, 1H), 8.94 (bs, 1H), 8.18 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7,01 (dd, J = 7.3, 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.62 (dd, J = 7.3, 7.7 Hz, 1H), 4.91 (bs, 2H), 4.78 (bs, 2H), 4.18 (m, 2H), 3.70 (m, 2H), 3.26 (s, 3H)

Example 151

Step 1: Methyl-4-{[3-(2-chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid ester (244)

[0302] To a stirred suspension at 0°C of methyl 4(aminomethyl)benzoate.HCl 2 (809 mg, 4.01 mmol) in anhydrous CH_2Cl_2 (25 ml) under nitrogen were successively added iPr_2NEt (1.91 ml, 10.95 mmol) and 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (1.00 g, 3.65 mmol). After 45 min, the reaction mixture was allowed to warm up to room temperature for 3 h. Then, the reaction mixture was concentrated, diluted with AcOEt, and successively washed with sat. NH_4Cl , H_2O , sat. $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to afford the title compound 244 (1.50 g, quantitative yield) as a colorless sticky foam. 1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (d, J = 7.9 Hz, 2H), 7.46-7.35 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.15-7.05 (m, 3H), 5.49 (bs, 1H), 4.46 (d, J = 5.7 Hz, 2H), 3.92 (s, 3H), 2.80 (s, 3H).

Step 2: 4-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid (245)

[0303] To a stirred solution at room temperature of 244 (1.45 g, 3.60 mmol) in THF (20 ml) was added a solution of LiOH. H_2O (453 mg, 10.80 mmol) in water (20 ml). After 20 h, the reaction

mixture was concentrated, diluted with water and acidified with 1N HCl until pH 6 in order to get a white precipitate. After 10 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound **245** (1.23 g, 3.15 mmol, 88% yield) as a white solid. 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): 8.69 (t, J = 5.9 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.70-7.58 (m, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.45-7.30 (m, 3H), 4.44 (d, J = 5.7 Hz, 2H), 2.72 (s, 3H). Step 3: 4(9-Chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzoic acid (**246**)

[0304] To a stirred suspension at room temperature of 245 (795 mg, 2.05 mmol) in anhydrous DMF (10 ml) was added a solution of NaOH (409 mg, 10.22 mmol) in anhydrous MeOH (5.1 ml). Then, the reaction mixture was warmed up to 40°C. After 3 days, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 5 in order to get a pale pinky precipitate. After 30 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 246 (679 mg, 1.84 mmol, 90% yield) as a pale pinky solid. 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): AB system (δ _A = 7.92, δ _B = 7.40, J = 8.4 Hz, 4H), 7.56 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 5.59 (bs, 2H), 2.95 (s, 3H). Step 4: *N*(2-Amino-phenyl)-4-(9-chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzamide (247)

[0305] The title compound 247 was obtained from 246 in one step following the same procedure as Example 1, steps 5. 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.65 (s, 1H), AB system (δ_A = 7.95, δ_B = 7.42, J = 8.1 Hz, 4H), 7.58 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 5.61 (bs, 2H), 4.91 (s, 2H), 2.97 (s, 3H).

Scheme 41

Example 152

Step 1: 4-(1H-Imidazol-2-yl)-benzoic acid (248)

[0306] To a stirred solution of 4-formylbenzoic acid (2.00 g, 12.3 mmol) in ammonium hydroxide (9 ml) was added glyoxal (2.86 ml, 20.0 mmol). The reaction mixture was stirred 16 h at room

temperature. 1N HCl was added to the reaction mixture to acidify to pH 5. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **248** (2.08 g, 83%) as a white solid. LRMS: 188.1 (Calc.); 189.1 (found).

Step 2: N(2-Amino-phenyl)-4-(1 Himidazol-2-yl)-benzamide (249)

[0307] The title compound 249 was obtained following the same procedure as Example 1, step 5. 1 H NMR (CDCl₃) δ (ppm): 1 H NMR: (DMSO) δ (ppm): 9.72 (bs, 1H), 8.07 (s, 4H), 7.26 (s, 2H), 7.18 (d, J = 7.9 Hz, 1H), 6.98 (dd, J = 7.5, 7.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H). MS: (calc.) 278.1; (obt.) 279.1 (MH)⁺.

Scheme 42

Example 153

Step 1: 4-Thiocarbamoylmethyl-benzoic acid (250)

[0308] To a stirred suspension of 4-cyanomethyl-benzoic acid (1.65 g, 10.24 mmol) and Et₃N (5 ml) in pyridine, H_2S was bubbled during 3 h. The reaction mixture was stirred 16 h at room temperature. Water was then added to the reaction mixture which was agitated for 1 h before acidifying to pH 6 with 1M HCl. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound **250** (2.08 g, 83%) as a white solid. ¹H NMR (DMSO) δ (ppm): 12.85 (bs, 1H), 9.53 (bs, 1H), 9.43 (bs, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 3.88 (s, 2H).

Step 2: 4-(4-Chloromethyl-thiazol-2-ylmethyl)-benzoic acid (251)

[0309] A solution of 250 (729 mg, 3.73 mmol) and 1,3-dichloroacetone (474 mg, 3.73 mmol) in THF (30 ml) was stirred at 40°C during 48h. The solvent was evaporated then the residue was dissolved in ethyl acetate, washed with brine, dried over anhydrous MgSO₄, filtered and

concentrated. The crude residue was purified by flash chromatography on silica gel (2-4% MeOH/CH₂Cl₂) to afford the title compound (827 mg, 83% yield) as a white solid. 1 H NMR (DMSO) $_{8}$ (ppm): 12.93 (bs, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 4.78 (s, 2H), 4.42 (s, 2H).

Step 3: N(2-Amino-phenyl)-4(4-morpholin-4-ylmethyl-thiazol-2-ylmethyl)-benzamide (252)

[0310] K_2CO_3 (599 mg, 4.33 mmol) was added to a solution of 251 (527 mg, 1.97 mmol) and morpholine (189 \square 1, 2.17 mmol) in THF (15 ml) was refluxed during 48h. The solvent was evaporated. The crude residue was purified by flash chromatography on silica gel (3-50% MeOH/CH₂Cl₂) to afford the title compound 252 (238 mg, 38% yield) as a pale yellow solid. LRMS: 318.2 (calc) 319.2 (found).

[0311] The title compound 252 was obtained following the same procedure as Example 1, step 5. 1H NMR (DMSO) δ (ppm): 9.63 (bs, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.15 (d, J = 8.1Hz, 1H), 6.97 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.1, 8.1 Hz, 1H), 4.90 (bs, 2H), 4.40 (s, 2H), 3.59-3.56 (m, 6H), 2.44-2.38 (m, 4H). LRMS: 408.2 (calc) 409.2 (found).

Example 154

Step 1: Methyl 3-[3-(4-methoxycarbonyl-benzyl)-ureido]-thiophene-2-carboxylate (253)

[0312] The procedure described by Nakao (K. Nakao, R. Shimizu, H. Kubota, M. Yasuhara, Y. Hashimura, T. Suzuki, T. Fujita and H. Ohmizu; *Bioorg. Med. Chem.* 1998, 6, 849-868.) was followed

to afford the title compound **253** (1.01 g, 91%) as a yellow solid. ¹H NMR (CDCl₃) δ (ppm): 9.55 (bs, 1H), 8.00-7.97 (m, 3H), 7.42-7.37 (m, 3H), 5.45 (t, J = 5.8 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H).

Step 2: 4-(2,4-Dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzoic acid (254)

[0313] To a suspension of 253 (422 mg, 1.21 mmol) in MeOH (15 ml) was added NaOH (145 mg, 3.63 mmol). The reaction mixture was heated at 60°C during 16 h. Water (1 ml) was then added and the reaction mixture was stirred for 1 more hour. The solvent was evaporated and the residue was dissolved in water and acidified to pH 5 with HCl 1M. The precipitate was filtered to afford the desired compound 254 (348 mg, 95%) as a white solid. LRMS: 302.0 (Calc.); 303.0 (found). Steps 3: N42-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (255)

[0314] The title compound 255 was obtained as a yellow solid (73%) following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 5. 1 H Ni⁄nR: (DMSO) δ (ppm): 9.61 (bs, 1H, NH), 8.22 (d, J = 5.5 Hz, 1H, CH), 7.91 (d, J = 8.2 Hz, 2H, CH), 7.43-7.40 (m, 3H, CH), 7.15 (d, J = 7.4 Hz, 1H, CH), 6.96 (dd, J = 7.6, 7.6 Hz, 1H, CH), 6.77 (d, J = 7.1 Hz, 1H, CH), 6.59 (dd, J = 7.4, 7.4 Hz, 1H, CH), 5.17 (s, 2H, NCH₂), 4.88 (bs, 2H, NH₂) 4.09 (q, J = 7.0, 2H, CH₂), 1.22 (t, J = 7.0, 3H, CH₃). LRMS: 420.1 (calc.); 421.0 (found).

Example 155

Step 1: 3H-Thieno[3,2-d]pyrimidin-4-one (256)

[0315] Methyl-3-amino-2-thiophene carboxylate (510 mg, 3.24 mmol) was dissolved in formamide (20 ml) and heated at 170°C 16h. The solvent was evaporated. The crude residue was then purified by flash chromatography on silica gel (2-4% MeOH/CH₂Cl₂) to afford the title compound 256 (157 mg, 32% yield). LRMS: 152.0 (Calc.); 152.9 (found).

Step 2: M2-Aminophenyl)-4-(4-oxo-4H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (257)

[O316] Following the procedure described in Example 85, step 1 but substituting the previous compound for 119, followed by Example 1, step 4, 5, the title compound 257 was obtained in 41% yield. 1 H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.70 (s, 1H), 8.22 (dd, J = 5.2, 0.5 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.44 (dd, J = 5.2, 0.6 Hz, 1H), 7.15 (d, J = 7.7 Hz, 1H), 6.96 (dd, J = 6.9, 6.9 Hz, 1H), 6.77 (d, J = 7.1Hz, 1H), 6.58 (dd, J = 7.0, 7.0 Hz, 1H), 5.31 (s, 2H), 4.87 (bs, 2H). MS: 376.1 (calc.); 377.1 (found).

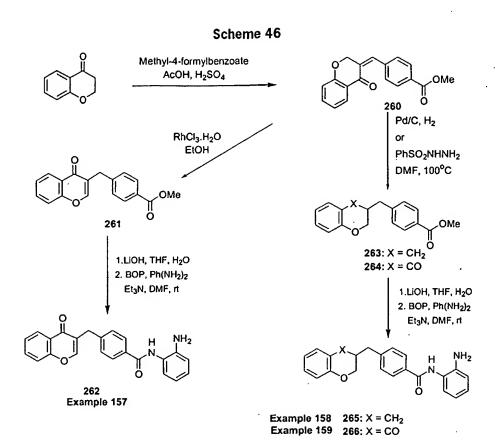
Scheme 45

Example 156

Step 1: Methyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (258)

[0317] The procedure described by Hozien (Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab and S. A. Ahmed; *Synht. Commun.*. 1996, 26(20), 3733-3755.) was followed to afford the title compound 258 (1.44 g, 17%) as a yellow solid. LRMS: 197.1 (Calc.); 200.1 (found). Steps 2: N-(2-Amino-phenyl)-4-(5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-ylmethyl)-benzamide (259)

[0318] Following the procedure described in Example 155, step 1, 2 but substituting 258 for 256, the title compound 259 was obtained as a white solid (55%). 1 H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.57 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 6.96 (dd, J = 7.6, 7.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.25 (s, 2H), 4.87 (bs, 2H), 2.39 (s, 3H), 2.37 (s, 3H). LRMS: 404.1 (calc); 405.0 (found).



Example 157

Step 1: Methyl 4-(4-oxo-chroman-3-ylidenemethyl)-benzoate (260)

[0319] Concentrated H₂SO₄ (2 ml) was slowly added to a solution of 4-chromanone (2.00 g, 13.50 mmol) and methyl-4-formylbenzoate (2.11 g, 12.86 mmol) in glacial acetic acid. The reaction mixture was stirred 16 h at room temperature. The solvent was concentrated to half volume the resulting precipitate was filtered and rinsed with ethyl acetate to afford the title compound **260** (3.11 g, 82%) as a purple solid. 1 H NMR: (DMSO) δ (ppm): 8.05 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.64-7.59(m, 3H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H), 3.89 (s, 3H).

Step 2: Methyl-4-(4-oxo-4H-chromen-3-ylmethyl)-benzoate (261)

[0320] Water (0.2 ml) and RhCl₃.H₂O (7 mg, 0.034 mmol) was added to a suspension of compound 260 (200 mg, 0.680 mmol) in EtOH (2 ml) and CHCL₃ (2 ml). The reaction mixture was stirred 16 h at 70°C. The reaction mixture was cooled down and diluted in ethyl acetate, washed with

brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (0.5-1% MeOH/CH₂Cl₂)to afford the title compound **261** (118 mg, 59%) as a white solid. 1 H NMR: (DMSO) δ (ppm): 8.45 (s, 1H), 8.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.83-7.77(m, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.50-7.43 (m3, 1H), 3.82 (s, 3H), 3.80 (s, 2H).

Step 3: N(2-Amino-phenyl)-4-(4-oxo-4H-chromen-3-ylmethyl)-benzamide (262)

[0321] The title compound 262 was obtained following the same procedure as Example 1, step 4, 5. 1 H NMR: (DMSO) δ (ppm): 9.56 (bs, 1H), 8.45 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.80 (dd, J = 7.5, 7.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.51-7.42 (m, 3H), 7.14 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 7.3, 7.3 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.86 (bs, 2H), 3.80 (s, 2H). LRMS: 370.1 (calc.); 371.1 (found).

Example 158

Step 2: Methyl 4-chroman-3-ylmethyl-benzoate (263)

[0322] Pd/C 10% was added to a suspension of 260 (200 mg, 0.68 mmol) in MeOH (40 ml) and DMA (10 ml) which was previously purged under vacuum. The reaction mixture was stirred during 4 h at room temperature. After evaporation of the MeOH, water was added to the oily residue and the precipitate obtained was filtered. The crude residue was then purified by flash chromatography on silica gel (5-8% AcOEt/Hex)to afford the title compound 263 (114 mg, 59%) as a white solid. LRMS: 282.1 (Calc.); 283.0 (found).

Step 3: N(2-Amino-phenyl)-4-chroman-3-ylmethyl-benzamide (265)

[0323] The title compound 265 was obtained following the same procedure as Example 1, steps 4 and 5. 1 H NMR: (acetone) δ (ppm): 9.06 (bs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.08-6.98 (m, 3H), 6.87 (d, J = 7.5 Hz, 1H),6.82-6.66 (m, 3H), 4.62 (s, 2H), 4.22-4.17 (m, 1H), 4.88-3.81 (m, 1H), 2.88-2.71 (m, 3H), 2.61-2.53 (m, 1H), 2.41-2.33 (m, 1H). LRMS: 358.2 (calc.); 359.1 (found).

Example 159

Step 2: Methyl 4-(4-oxo-chroman-3-ylmethyl)-benzoate (264)

[0324] A suspension of 260 (400 mg, 1.36 mmol) and benzenesulfonyl hydrazine (702 mg, 4.08 mmol) in DMF (7 ml) was stirred at 100°C during 48h. The solvent was evaporated and the

residue was diluted in AcOEt, washed with NH₄Cl sat., brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5% AcOEt/HEx)to afford the title compound **264** (170 mg, 42%) as a white solid. LRMS: 296.1 (Calc.); 297.0 (found).

Step 3: N(2-Amino-phenyl)-4-(4-oxo-chroman-3-ylmethyl)-benzamide (266)

[0325] The title compound 266 was obtained following the same procedure as Example 1, steps 4 and 5. 1 H NMR: (acetone) δ (ppm): 9.62 (bs, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.0, 7.0 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.17-7.04 (m, 3H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 4.88 (s, 2H), 4.44-4.39 (m, 1H), 4.28-4.21 (m, 1H), 2.26-3.21 (m, 2H), 2.83-2.74 (m, 1H). LRMS: 372.1 (calc.); 372.1 (found).

Scheme 47

Example 160

Step 1: Methyl 4(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzoate (266)

[O326] Et₃N (3.18 ml, 22.8 mmol) was added to a stirring solution of 2-H-1,4-benzoxazin-3-(4H)one (2.50 g, 16.8 mmol) and methyl 4-formylbenzoate (4.59 g, 27.5 mmol) in Ac₂O (20 ml). The reaction mixture was refluxed 16h. After this mixture was cooled for 3 days, the solid was filtered and rinsed with ethyl acetate to afford the title compound **266** (657 mg, 13%) as a yellow solid. LRMS: 295.1 (Calc.); 296.0 (found).

Step 2: Methyl 4-(3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl)-benzoate (267)

[0327] The title compound 267 was obtained following the same procedure as Example 158, step 2. LRMS: 297.1 (Calc.); 298.1 (found).

Step 3: N(2-Amino-phenyl)-4-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (269)

[O328] The title compound 269 was obtained from 267 following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 4, 5. 1 H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.11-6.91 (m, 4H), 6.77 (d, J = 7.0 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.95-4.91 (m, 1H), 4.89 (bs, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.28-3.22 (m, 1H), 3.17-2.89 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H). LRMS: 401.2 (calc.); 402.1 (obt.).

Example 161

Step 1: N(2-Amino-phenyl)-4(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (270)

[0329] The title compound 270 was obtained from 267 following the same procedure as Example 1, step 4, 5. 1 H NMR: (DMSO) δ (ppm): 10.74 (bs, 1H), 9.61 (bs, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.99-6.85 (m, 5H), 6.78 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.92-4.89 (m, 3H), 3.29-3.23 (m, 1H), 3.15-3.07 (m, 1H). MS: (calc.) 373.1; (obt.) 374.1 (MH) $^{+}$.

Scheme 48

Example 162

Step 1: Methyl 4(1-oxo-indan-2-ylmethyl)-benzoate (271)

[0330] A 2M LDA solution in THF (4.16 ml, 8.32 mmol) was added to a solution of indanone (1.00 g, 7.57 mmol) in THF (10 ml) at –60°C. The solution was slowly warmed to 0°C during a period of 15 min. and was agitated for 15 more min. The reaction was then cooled to –78°C and a solution of methyl-4-bromobenzoate (1.73 g, 7.57 mmol) was slowly added. The solution was slowly warmed to –20°C and stirred during 4 hours. The reaction mixture was quenched with HCL 1M and the solvent was evaporated. The residue was diluted in ethyl acetate, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5-20% AcOEt/HEx)to afford the title compound **271** (245 mg, 17%) as a white solid. LRMS: 280.1 (Calc.); 281.1 (found).

Step 2: N(2-Amino-phenyl)-4-(1-oxo-indan-2-ylmethyl)-benzamide (272)

[0331] The title compound 272 was obtained following the same procedure as Example 1, step 4, 5. 1 H NMR: (DMSO) δ (ppm): 9.59 (bs, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.69-7.64 (m, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.45-7.40 (m, 3H), 7.16 (d, J = 8.2 Hz, 1H), 6.96 (dd, J = 7.3, 7.3 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.87 (bs, 2H), 3.23-3.14 (m, 3H), 2.85-2.81 (m, 2H). LRMS: 356.1 (calc.); 357.2 (found).

Example 163

Step 1: 4-(1-Oxo-indan-2-ylidenemethyl)-benzoic acid (273)

[0332] To a suspension of indanone (2.00 g, 15.1 mmol) and 4-carboxybenzaldehyde (1.89g, 12.6 mmol) in EtOH (10 ml) was added KOH (1.77 g, 31.5 mmol) at 0°C. The reaction mixture was stirred 30 min at 0°C then at room temperature for 16 h. The solvent was evaporated and the residue was dissolved in water, acidified to pH 5 with HCl 1 M. The precipitate was filtered and rinsed with water to afford the title compound 273 (2.27 g, 57%) as a yellow solid. LRMS: 264.1 (Calc.); 265.0 (found).

Step 2: N(2-Amino-phenyl)-4-(1-oxo-indan-2-ylidenemethyl)-benzamide (274)

[0333] The title compound 274 was obtained following the same procedure as Example 1, step 5. LRMS: 354.1 (Calc.); 355.0 (found).

Step 3: N(2-Amino-phenyl)-4-(1-hydroxy-indan-2-ylmethyl)-benzamide (275)

[0334] To a suspension of 274 (300 mg, 0.85 mmol) in MeOH (8 ml) and water (1 ml) was added NaBH₄ (75 mg, 1.95 mmol). The reaction mixture was stirred at 50°C 16h and cooled down. Water was added to the solution and the precipitated was filtered and rinsed with cold water to afford the title compound 275 (224 mg, 74%) as a white solid. 1 H NMR: (acetone) δ (ppm): 9.05 (bs, 1H), 8.00 (dd, J = 8.2, 2.7 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 1H), 7.38-7.30 (m, 2H), 7.22-7.12 (m, 3H), 7.01 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.87 (dd, J = 8.0, 1.1 Hz, 1H), 6.68 (dd, J = 7.6, 7.6 Hz, 1H), 4.98 (t, J = 5.8 Hz, 0.4H), 4.89 (t, J = 6.7 Hz, 0.6H), 4.63 (bs, 2H), 4.45 (d, J = 6.9 Hz, 0.6H), 4.06 (d, J = 6.0 Hz, 0.4H), 3.30-3.19 (m, 1H), 2.88-2.48 (m, 3H, CH₂). LRMS: 358.2 (calc.); 359.1 (found).

Example 164

Step 1: 4(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-benzoic acid (276)

[0335] To a solution of NaH (60% in mineral oil, 250 mg, 6.3 mmol) at 0°C acetyl acetone (0.646 ml, 6.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester **2** (1.2 g, 5.2 mmol). The reaction mixture stirred 1 hour at room temperature and refluxed for 2 hours. Phenyl hydrazine (0.51 ml, 5.2 mmol) was added and the reaction mixture refluxed for an additional hour. THF was removed in vacuum and the oily residue was partitioned between water and ethyl acetate. Organic layer was separated, dried, evaporated and purify by chromatography on a silica gel column, eluent EtOAc – hexane (1:1) to produce an oily material (800mg) which was treated with a solution of

NaOH (0.8 g, 20 mmol) in 20 ml water for 1 hour at room temperature. The following steps, - acidification with HCl (pH 6), extraction of the resultant emulsion with ethyl acetate, drying the extract with sodium sulfate, evaporation and column chromatography (eluent EtOAc – hexane, 1:1) afforded 390 mg of a mixture of **276** (the title compound) and **278** (molar ratio 1:2). [M-1]⁺ 307.0 and 191.1. This mixture was taken for the next step as is.

Step 2. N-(2-Amino-phenyl)-4-(3,5-dimethyl-1-phenyl-1 H-pyrazol-4-ylmethyl)-benzamide (277)

[0336] Following a procedure analogous to that described in Example 92, step 2, but substituting 276 for 143, the title compound 277 was obtained in 25% yield (purified by chromatography using as eluent EtOAc - hexane, 1:1). 1 H NMR: (300 MHz, DMSO-d₆, δ (ppm): 9.64 (s, 1H); 7.97 (d, J = 7.6 Hz, 2H), 7.42-7.56 (m, 5H), 7.37 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 4.93 (s, 2H), 3.92 (s, 2H), 2.34 (s, 3H), 2.18 (s, 3H).

Example 165

Step 1: 4-(3-Oxo-butyl)-benzoic acid (278)

[0337] To a solution of acetyl acetone (5.0 ml, 49 mmol) at room temperature NaOMe (25% wt, 10.8 ml, 47.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester 2 (9.0 g, 39.3 mmol). The reaction mixture refluxed 3 hours, cooled to the room temperature and acidified with HCl (pH 1-2). Evaporation of the resultant solution yielded a residue, which was refluxed in a mixture of glacial AcOH (50 ml) and conc. HCl (25 ml) for 4 hours. Acids were removed in vacuum and the residue was triturated with water to form a crystalline material, which was collected by filtration and dried to afford 278 (6.72 g, 80% yield). [M-1] 191.1.

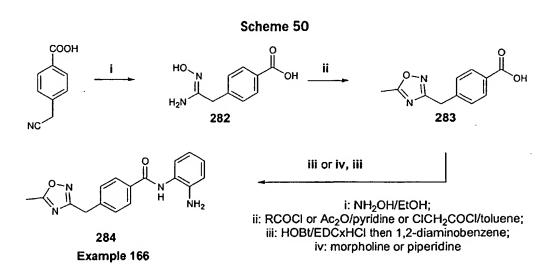
Step 2. 4-(5-Amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 279

[0338] To a refluxing suspension of 4-(3-oxo-butyl)-benzoic acid 278 (700 mg, 3.65 mmol), malonodinitrile (241 mg, 3.65 mmol) and sulfur (130 mg, 3.65 mmol) in 20 ml EtOH, diethylamine (0.5 ml, 4.8 mmol) was added. The reaction mixture refluxed 1 hour, cooled to the room temperature, acidified with conc. HCl (pH 4-5) and evaporated to yield a solid residue. This material was partitioned between water and ethyl acetate, organic layer was separated, dried, evaporated and chromatographed on a silica gel column, eluent EtOAc-hexane, 1:1, to afford the title compound 279 (300 mg, 30% yield). 1 H NMR: (300 MHz, DMSO-d₆; $^{\circ}$ ppm): 7.87 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.98 (s, 2H), 3.92 (s, 2H), 2.03 (s, 3H).

Step 3. 4-(5-Acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 280

[0339] To a solution of 4-(5-amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 279 (230 mg, 0.86 mmol) in a solvent mixture acetone (5 ml) – dichloromethane (5 ml) at room temperature acetyl chloride (0.305 ml, 4.3 mmol) was added. After 2 hours of stirring at the same conditions a precipitate of the title compound 280 formed which was collected and dried (200 mg, 75% yield). [M-1] 313.1.

Step 4: $N(2-Amino-phenyl)-4-(5-acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)- benzamide (281) [0340] Following a procedure analogous to that described in Example 92, step 2, but substituting 280 for 143, the title compound 281 was obtained in 25% yield. 1H NMR (DMSO) <math>\delta$ (ppm): 9.61 (s, 1H); 7.91 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 6.6 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.10 (s, 2H), 2.19 (s, 3H), 2.16 (s, 3H). [M+1] 405.0.



Example 166

Step 1. 4(N-Hydroxycarbamimidoylmethyl)-benzoic acid (282)

[0341] A suspension of 4-cyanomethyl benzoic acid (2.07 g, 12.86 mmol), NH₂OH.HCl (1.79 g, 25.71 mmol) and potassium hydroxide (2.16 g, 38.57 mmol) in 70 ml ethanol refluxed for 36 hours, poured into 100 ml water and acidified with conc. HCl (pH 5-6). EtOH was removed in vacuum and the remaining suspension was treated with another 100 ml water. A precipitate formed which was collected and dried to afford the title compound 282. [M+1]195.1.

Step 2. 4(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzoic acid (283)

[0342] A solution of 4-(N-hydroxycarbamimidoylmethyl)-benzoic acid 282 (388 mg, 2.0 mmol) in pyridine (8 ml) was treated with acetic anhydride (0.283 ml, 3.0 mmol). The resultant solution refluxed 6 hours, evaporated in vacuum and the remaining solid was triturated with water, collected by filtration, dried and purified by chromatography on a silica gel column, eluent EtOAc, EtOAc-MeOH (10:1) and finally EtOAc-MeOH (1:1), to produce 283 (164 mg, 38% yield).[M-1] 217.1

Step 3. N(2-Amino-phenyl)-4-(5-methyl-[1, 2, 4]oxadiazol-3-ylmethyl)-benzamide (284)

[0343] For the preparation of the title compound 284, a procedure analogous to that described in Example 92, step 2, but substituting 283 for 143, the title compound 284 was obtained. ^{1}H NMR: (DMSO) δ (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 4.92 (s, 2H), 4.14 (s, 2H), 2.55 (s, 3H). [M+1]* 309.2

Scheme 51

i: Acetyl acetone/EtOH;

ii: HOBt/EDCxHCI then 1,2-diaminobenzene;

Example 167

Step 1: 4-(3,5-Dimethyl-pyrazol-1-yl)-benzoic acid (285)

[0344] A solution of 4-hydrazino-benzoic acid (0.60 g, 3.95 mmol) and acetyl acetone (0.405 ml, 3.95 mmol) in ethanol (20 ml) refluxed for 1 hour. Ethanol was removed in vacuum and the remaining solid was triturated with water and collected by filtration to produce 285 (0.71 mg, 83% yield). [M-1] 215.1.

Step 2. N-(2-Amino-phenyl)-4-(3,5-dimethyl-pyrazol-1-yl)-benzamide (286)

[0345] For the preparation of the title compound 286, a procedure analogous to that described in Example 92, step 2, but substituting 285 for 143, the title compound 286 was obtained in 34% yield (purified by chromatography using as eluent CH₂Cl₂methanol, 19:1). ¹H NMR: (DMSO) δ (ppm):

9.73 (s, 1H); 8.09 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 4.92 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H). [M+1]⁺ 303.3

- a. 2.5% $Pd(OAc)_2$ / nBu_4NCI (1 eq) / KOAc (3 eq) / 2.5% PPh_3 / DMF / $80^{\circ}C$
- b. 3-4% Pd(OAc)₂ / 9% PPh₃ / Ag₂CO₃ (2 eq) / CH₃CN / 80°C
- c. LiOH ' H₂O / THF-H₂O (2:1)
- d. 1,2-phenylenediamine / BOP / Et₃N / DMF
- e. PtO2 / H2 (1 atm) / AcOEt

Example 168

Step 1: 2(3,4,5-Trimethoxy-phenyl)-2,3-dihydro-furan (287)

[0346] To a solution of 5-iodo-1,2,3-trimethoxybenzene (900 mg, 3.06 mmol) and 2,3-dihydrofuran (1.16 mL, 15.3 mmol) in dry DMF (8 mL) were added PPh₃ (20 mg, 0.077 mmol), KOAc

(901 mg, 9.18 mmol), n-Bu₄NCI (850 mg, 3.06 mmol) and Pd(OAc)₂ (17 mg, 0.077 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was diluted with AcOEt and water. After separation, the organic layer was washed with brine, dried over anhydrous Na2SO4, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 20/80) to afford the title compound 287 (311 mg, 1.32 mmol, 43% yield). ¹H NMR: (300 MHz, CDCl₃) δ (ppm): 6.59 (s, 2H), 6.45 (m, 1H), 5.45 (dd, J = 10.5, 8.4 Hz, 1H), 4.97 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.06 (m, 1H), 2.62 (m, 1H).

Step 2: 4[5-(3,4,5-Trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzoic acid ethyl ester (288)

[0347] To a solution of 287 (200 mg, 0.846 mmol) and 4-lodo-benzoic acid ethyl ester (468 mg, 1.69 mmol) in dry acetonitrile (4 mL) were added PPh₃ (20 mg, 0.076 mmol), Ag₂CO₃ (467 mg, 1.69 mmol) and Pd(OAc)₂ (7 mg, 0.03 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was filtered through celite and washed with AcOEt. Water was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 30/70) to afford the title compound 288 (280 mg, 0.728 mmol, 86% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.05 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 6.18-5.95 (m, 4H), 4.38 (q, J = 7.0 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 1.39 (t, J = 7.0 Hz).

Step 3: N(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide (289)

Following a procedure analogous to that described in Example 1, step 4, 5, but [0348] substituting 288 for 6, the title compound 289 was obtained in 48% yield. ¹H NMR (DMSO) δ (ppm): 8.00 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7= 7.5 Hz, 1H), 6.92-6.82 (m, 2H), 6.61 (s, 2H), 6.14-5.99 (m, 4H), 3.89 (s, 6H), 3.84 (s, 3H).

Example 169

Step 1: N(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzamide. (290)

[0349] To a degazed solution of 289 (43 mg, 0.096 mmol) in AcOEt (4 mL) was added PtO₂ (3 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature under a 1 atm pressure of H₂ for 16 h. The reaction flask was purged with N₂ then the reaction mixture was filtered through celite, rinsed with MeOH and concentrated. The crude residue was purified three times by flash chromatography on silica gel (MeOH/DCM: 2/98, AcOEt/DCM: 30/70 and AcOEt/CHCl3: 30/70) to afford the title compound 290 (10 mg, 0.22 mmol, 23% yield). ¹H NMR (CDCl₃) δ (ppm): 8.10 (s. 1H), 7.91 (d, $J = 8.0 \, \text{Hz}$, 2H), 7.50 (d, $J = 8.0 \, \text{Hz}$, 2H), 7.34 (d, $J = 7.5 \, \text{Hz}$, 1H), 7.10 (t, $J = 7.5 \, \text{Hz}$, 1H), 6.96-6.85 (m, 2H), 6.64 (s, 2H), 5.33 (t, J = 7.0 Hz, 1H), 5.21 (t, J = 7.0 Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 2.59-2.40 (m, 2H), 2.09-1.88 (m, 2H).

Scheme 53

- a. Tributyl(vinyl)tin / Pd(PPh₃)₄ / Toluene / 100°C
- b. m-CPBA / CHCl₃ / r.t.
- c. 3,4,5-trimethoxyaniline / CoCl₂ / CH₃CN
- d. TFA / DCM
- e. 1,1'-carbonyldiimidazole / DCM / r.t.
- f. 1,1'-carbonyldiimidazole / Et₃N / Toluene / THF / 90°C

Example 169

Step 1: [2-(4-Vinyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (291)

[0350] Following a procedure analogous to that described in Example 143, step 2, but substituting **184** for **221**, the title compound **291** was obtained in 90% yield as a dark yellow oil. 1 H NMR: (300 MHz, CDCl₃) δ (ppm): 9.18 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.30-7.10 (m, 3H), 6.89 (s, 1H), 6.77 (dd, J = 17.4, 11.0 Hz, 1H), 5.87 (d, J = 17.4 Hz, 1H), 5.39 (d, J = 11.0 Hz, 1H), 1.52 (s, 9H).

Step 2: [2-(4-Oxiranyl-benzoylamino)-phenyll-carbamic acid tert-butyl ester (292)

[0351] To a solution of 291 (4.1 g, 12.1 mmol) in dry CHCl₃ (60 mL) was added *m*-CPBA 70% (3.6 g, 14.5 mmol). The reaction mixture was stirred at room temperature for 5 h then additional *m*-CPBA (0.6 g, 2.4 mmol) was added and the stirring continued for 1 h. A further amount of *m*-CPBA (0.6 g, 2.4 mmol) was added and the reaction mixture was stirred for 16 h. Chloroform and a 10% solution of NaHCO₃ were added and the phases were separated. The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 1/3) to afford the title compound 292 (2.86 g, 8.07 mmol, 66% yield). ¹H NMR (300 MHz, CDCl₃) & (ppm): 9.20 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.86-7.75 (m, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.26-7.10 (m, 3H), 6.84-6.70 (m, 1H), 3.93 (t, J = 3.0 Hz, 1H), 3.20 (t, J = 5.0 Hz, 1H), 2.80 (dd, J = 5.0, 3.0 Hz, 1H), 1.52 (s, 9H). Step 3: (2-(4-[1-Hydroxy-2-(3.4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (295) and (2-(4-[2-Hydroxy-1-(3.4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (293)

[0352] To a stirred solution of $CoCl_2$ (8 mg, 0.06 mmol) in dry acetonitrile (10 mL) was added 292 (1 g, 2.8 mmol) followed by 3,4,5-trimethoxyaniline (516 mg, 2.8 mmol) and the reaction mixture was allowed to react for 16 h at room temperature then it was heated at 60°C for 5 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/Hexane: 1/1) to afford compounds 293 and 295 (combined: 1.07 g, 1.99 mmol, 71% yield, ratio 292/295 = 5/1) which can be separated by flash chromatography on silica gel (AcOEt/Hexane: 1/1). ¹H NMR (300 MHz, CDCl₃) δ (ppm): Compound 292: 9.21 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.28-7.10 (m, 3H), 6.90 (s, 1H), 5.83 (s, 2H), 4.54-4.44 (m, 1H), 3.93 (dd,

J = 8.1, 3.9 Hz, 1H), 3.84-3.72 (m, 1H), 3.71 (s, 3H), 3.66 (s, 6H), 1.47 (s, 9H). Compound **295**: 9.22 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.30-7.21 (m, 3H), 6.88 (s, 1H), 6.15 (s, 2H), 5.16-5.06 (m, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.50-3.25 (m, 2H), 1.51 (s, 9H).

Step 4: $N(2-Amino-phenyl)-4-[2-hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzamide (294) [0353] Following a procedure analogous to that described in Example 42, step 3, but substituting 293 for 46, the title compound 294 was obtained in 50% yield. <math>^1H$ NMR (DMSO) δ (ppm): 8.36 (s, 1H), 7.74 (d, J = 6.9 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.72 (m, 2H), 5.69 (s, 2H), 4.34 (m, 1H), 4.02-3.52 (m, 2H), 3.66 (s, 3H), 3.57 (s, 6H).

Example 170

Step 1: N(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-4-yl]-benzamide (296)

[0354] To a solution of 293 (200 mg, 0.372 mmol) in toluene (5 mL) and THF (1 mL) was added 1,1'-carbonyldiimidazole (72 mg, 0.45 mmol) followed by Et₃N (156 μ L, 1.12 mmol) and the mixture was stirred at room temperature for 5 h then at 90°C for 48 h. The reaction mixture was diluted with AcOEt, a solution of *sat.* NH₄Cl was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (DCM/AcOEt: 80/20) to afford the desired compound (120 mg, 0.21 mmol, 57% yield). ¹H NMR (DMSO) δ (ppm): 9.37 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.25-15 (m, 3H), 6.88 (s, 1H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.79 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 8.7, 6.0 1H), 3.75 (s, 3H), 3.72 (s, 6H), 1.47 (s, 9H).

[0355] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **296** was obtained in 81% yield.). ^{1}H NMR (DMSO) δ (ppm): 8.03 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.78 (t, J = 8.7 Hz, 1H), 4.18 (dd, J = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H).

Example 171

Step 1: N42-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-5-yl]-benzamide (297) [0356] To a solution of 295 (130 mg, 0.242 mmol) in DCM (2 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol) and the mixture was stirred at room temperature for 16 h. DCM was removed under reduced pressure, AcOEt and a solution of *sat.* NH₄Cl were added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (Hexane/AcOEt: 30/70) to afford the desired compound (80 mg, 0.14 mmol, 58% yield). 1 H NMR (DMSO) δ (ppm): 9.39 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.26-7.12 (m, 3H), 6.86-6.74 (m, 3H), 5.70 (t, J = 8.4 Hz, 1H), 4.24 (t, J = 8.7 Hz, 1H), 3.97-3.87 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 1.52 (s, 9H).

[0357] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for **46**, the title compound **297** was obtained in 94% yield.). 1 H NMR (DMSO) δ (ppm): 8.38 (s, 1H), 7.97 (d, J = 7.5 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.97-6.87 (m, 2H), 6.79 (s, 2H), 5.66 (t, J = 8.1 Hz, 1H), 4.41 (t, J = 9.0 Hz, 1H), 3.91 (t, J = 7.8 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H).

a. CeCl₃ heptahydrate / NaN₃ / CH₃CN - H₂O (9:1) / reflux

305 Example 173

- b. H₂ / Pd/C (10%) / MeOH
- c. 3,4-dimethoxybenzoyl chloride / $\rm Et_3N$ / DCM / -20 $^{\rm o}$ C to r.t.
- d. Burgess reagent / THF / 70°C
- e. TFA / DCM

301

Example 172

Example 172

Step 1: {2-[4-(1-Azido-2-hydroxy-ethyl)-benzoylaminol-phenyl}-carbamic acid tert-butyl ester (298) and {2-[4-(2-Azido-1-hydroxy-ethyl)-benzoylaminol-phenyl}-carbamic acid tert-butyl ester (302)

[O358] To a solution of 292 (210 mg, 0.59 mmol) in acetonitrile (9 mL) and water (1 mL) was added CeCl₃ heptahydrate (110 mg, 0.296 mmol) followed by NaN₃ (42 mg, 0.65 mmol). The reaction mixture was refluxed for 3 h then acetonitrile was removed under reduced pressure. The residue was diluted with DCM, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. Purification by flash chromatography on silica gel (AcOEt/Hexane: 1/1) afforded a 1:1 mixture of title compounds 298 and 302 (combined: 187 mg, 0.47 mmol, 80% yield) which were separated by flash chromatography on silica gel (AcOEt/Hexane: 2/5). Compound 298: 1 H NMR: (300 MHz, CDCl₃/CD₃OD) δ (ppm): 7.95 (d, J = 8.1 Hz, 2H), 7.70-7.63 (m, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.36-7.29 (m, 1H), 7.24-7.14 (m, 2H), 4.69 (dd, J = 7.5, 4.8 Hz, 1H), 3.80-3.65 (m, 2H), 1.49 (s, 9H). Compound 302: 1 H NMR: (300 MHz, CDCl₃) δ (ppm): 9.28 (s, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.25-7.08 (m, 3H), 7.01 (s, 1H), 4.87 (dd, J = 6.9, 5.1 Hz, 1H), 3.47-3.38 (m, 2H), 3.32-3.21 (bs, 1H), 1.50 (s, 9H).

Step 2: {2-I4-(1-Amino-2-hydroxy-ethyl)-benzoylaminol-phenyl)-carbamic acid tert-butyl ester (299) [0359] To a solution of 298 (156 mg, 0.39 mmol) in MeOH (2 mL) was added Pd/C 10% (20 mg, 0.02 mmol). The reaction mixture was stirred under a 1 atm pressure of H₂ at room temperature for 16 h then it was purged with N₂. The palladium was removed by filtration through celite and the MeOH was evaporated under reduced pressure to afford the title compound 299 (88 mg, 0.24 mmol, 60% yield), which was used without purification. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.24 (s, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.31-7.10 (m, 3H), 7.06-6.94 (m, 1H), 4.12 (dd, J = 7.5, 4.5 Hz, 1H), 3.74 (dd, J = 7.8, 5.4 Hz, 1H), 3.64-3.51 (m, 1H), 2.64 (s, 3H), 1.49 (s, 9H).

Step 3: (2-(4-[1-(3,4-Dimethoxy-benzoylamino)-2-hydroxy-ethyl]-benzoylamino)-phenyl)-carbamic acid tert-butyl ester (300)

[0360] To a stirred solution of 299 (88 mg, 0.24 mmol) in dry DCM (2 mL) at -20°C was added 3,4-dimethoxybenzoyl chloride (50 mg, 0.25 mmol) followed by Et₃N (37 μ L, 0.26 mmol). The reaction mixture was allowed to warm up to room temperature then was stirred for 48 h. A solution of sat. NH₄Cl was added, followed by DCM and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 4/96) to afford title compound 300 (91 mg, 0.17 mmol, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.29 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.46 (m, 7H), 6.80 (d, J = 8.1 Hz, 1H), 5.20-5.10 (m, 1H), 3.95-3.78 (m, 2H), 3.88 (s, 3H) 3.84 (s, 3H), 1.47 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-4-yl]-benzamide (301) [0361] To a solution of 300 (91 mg, 0.17 mmol) in dry THF (2 mL) was added the Burgess reagent (44 mg, 0.19 mmol) and the mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 3/97) to afford the Boc-protected intermediate (75 mg, 0.14 mmol, 85% yield). ¹H NMR (CDCl₃) δ (ppm): 9.31 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.0 Hz, 1H), 7.23-7.08 (m, 3H), 6.93 (d, J = 8.7 Hz, 1H), 5.43 (t, J = 9.0 Hz, 1H), 4.84 (t, J = 9.3 Hz, 1H), 4.26 (t, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.50 (s, 9H).

[0362] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 301 was obtained in 82%. 1 H NMR (CDCl₃) δ (ppm): 8.01 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.65 (dd, J = 8.4, 1.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 6.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 5.43 (dd, J = 9.7, 8.4 Hz, 1H), 4.83 (dd, J = 9.7, 8.4 Hz, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

Example 173

Step 1: {2-[4-(2-Amino-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (303)

[0363] The title compound 303 was obtained in 94% yield from 302 following the same procedure as in Example 172, step 2. The compound 303 was used directly for next step without purification.

Step 2: 2-[4-[2-(3,4-Dimethoxy-benzoylamino)-1-hydroxy-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (304)

[0364] The title compound 304 was obtained in 40% yield from 303 and 3,4-dimethoxybenzoyl chloride following the same procedure as in Example 172, step 3. 1 H NMR (CDCl₃) δ (ppm): 9.31 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 8.1 Hz), 7.30-7.06 (m, 4H), 7.00-6.93 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.89-4.82 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85-3.73 (m, 1H), 3.44-3.32 (m, 1H), 1.46 (s, 9H).

Step 3: N(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-5-yl]-benzamide (305)

[0365] Following a procedure analogous to that described in Example 172, step 4, 5, but substituting 304 for 300, the title compound 305 was obtained in 63%. 1 H NMR (CDCl₃) δ (ppm): 8.02 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 8.4, 1.8 Hz, 1H), 7.60 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 5.74 (dd, J = 10.0, 7.8 Hz, 1H), 4.51 (dd, J = 14.5, 10.0 Hz, 1H), 4.00-3.90 (m, 7H).

Scheme 57

Example 178

STEP 1:[2-(4-FORMYL-BENZOYLAMINO)-PHENYL]-CARBAMIC ACID TERT-BUTYL ESTER (315)

[0366] To a suspension of 4-carboxybenzaldehyde (6 g, 40 mmol) in dichloromethane (10 mL) was added thionyl chloride (4.1 mL, 56 mmol, 1.4 eq), followed by DMF (1 mL) dropwise. The mixture was refluxed for 4 hours and excess of thionyl chloride and DMF were removed under reduced pressure. To a solution of (2-aminophenyl)-carbamic acid *tert*-butyl ester (8.32 g, 40 mmol, 1 eq) in dichloromethane (80 mL), stirred at 0°C, was added a suspension of 4-formyl benzoyl chloride in dichloromethane (20 mL), followed by diisopropyl ethylamine (3.61 mL, 20 mmol, 1 eq). The mixture was stirred for 30 minutes at 0°C then at room temperature for 30 minutes. The crude residue was diluted with dichloromethane (300 mL) and washed with water. The combined organic layers were dried (MgSO₄), filtered and concentrated under vacuo. The crude residue was purified by column chromatography on silica gel (elution 20% ethyl acetate in hexane) to give 6.1 g (45% yield) of anilide 315. 1 H NMR (CDCl₃): δ 10.18 (s, 1H), 9.64 (brs, 1H), 8.20 (d, J = 7.9 Hz, 2H), 8.06 (d, J = 7.9 Hz, 2H), 7.96 (d, J = 7.9 Hz, 1H), 7.28-7.38 (m, 1H), 7.24 (d, J = 4.4 Hz, 1H), 6.84 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 1.58 (s, 9H).

Step 2: (2-{4-[(3,4-Dimethoxyphenylamino}-Methyl]-Benzoylamino}-Phenyl)-Carbamic Acid Tert-Butyl Ester (316)

[0367] Following a procedure analogous to that described in Example 144, step 3, but substituting the previous compound for 226, the title compound 316 was obtained in quantitative yield. ¹H NMR (CDCI₃): δ 9.21 (brs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.20-7.34 (m, 3H), 6.89 (brs, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.23 (dd, J = 2.6, 8.3 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H). Step 3: N(2-Aminophenyl)-4-[1-(3,4-dimethoxyphenyl)-3-(4-methylsulfanylphenyl)-ureidomethyl]-

benzamide 317

[0368] To a solution of anilide 316 (500 mg, 1.047 mmol) in chloroform/THF (1:1, 10 mL) was added isocyanate (169 µL, 1.205 mmol, 1.15 eq). The mixture was stirred overnight at room temperature under nitrogen and the crude residue was concentrated and purified by column chromatography on silica gel (elution 40% ethyl acetate in hexane) to give 606 mg (90% yield) of the desired compound. ¹H NMR (CDCI₃): δ 9.25 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.20-7.36 (m, 6H), 6.93 (d, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6. = 2.2, 8.3 Hz, 1H, 6.68 (dd, J = 2.6 Hz, 1H), 6.33 (s, 1H), 5.0 (s, 2H), 3.97 (s, 3H), 3.85 (s, 3H),2.51 (s, 3H), 1.57 (s, 9H).

[0369] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 317 was obtained in 85% yield. ¹H NMR (DMSO-d₆): δ 10.14 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.93 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39 (d, J = 7.5 Hz, 1H), 7.10-7.30 (2m, 5H), 6.97 (dd, J = 2.2, 8.35 Hz, 1H), 6.77 (dd, J = 2.2, 8.35 Hz, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.48 (s, 3H).

Scheme 58

Example 17

Example 179

Step 1: N(2-Amino-phenyl)-6-chloro-nicotinamide (318)

[0370] Following the procedure described in Example 42, step 2, the title compound 318 was obtained in 80% yield. LRMS = calc:246.69, found:247.7.

Step 2: N-(2-Amino-phenyl)-6-(quinolin-2-ylsulfanyl)-nicotinamide (319)

[0371] Following the procedure described in Example 45, step 1 but substituting 318 for 3,4,5-trimethoxybenzylamine, the tite compound 319 was obtained in 20% yield. 1 H NMR: (CD₃OD-d6) δ (ppm): 9.08 (d, J= 1.9 Hz, 1H), 8.35-8.25 (m, 2H), 7.99-7.56 (m, 7H), 7.23 (dd, J= 1.2, 7.9 Hz, 1H), 7.12 (dd J=1.4, 7.9, 14.0 Hz, 1H), 6.93 (dd, J=1.2, 8.0Hz, 1H), 6.79 (ddd, J=1.4, 7.7, 13.7 Hz, 1H).

Scheme 59

Step 1: 4-I(4-Morpholin-4-yl-phenylamino)-methyll-benzoic acid (402a).

[0372] A suspension of 4-formylbenzoic acid (2.53g; 16.8 mmol; 1 eq), 4-morpholinoaniline (3g; 16.8 mmol; 1 eq) and Bu₂SnCl₂ (510 mg; 1.68 mmol; 0.1 eq) in dry THF (20 ml) was treated with PhSiH₃ (3.31ml; 16.8 mmol; 1 eq) at room temperature for 12 h. The reaction was filtered and the solid product was washed with MeOH. The yield of the reaction was 5.25g (99%). LRMS: calc 312.37; found: 313.2.

Step 2: N(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide (402)

[0373] To a solution of acid 402a (2.61g; 8.36 mmol; 1 eq), 1,2-phenylenediamine (903 mg; 8.36 mmol; 1 eq) and BOP (3.70g; 8.36 mmol; 1 eq) in dry DMF (20 ml) was added Et₃N (4.64ml; 33.4 mmol; 4 eq). After stirring overnight most of the DMF was removed under reduced pressure and chromatographed (Hex:EtAcO: 1:2/ EtAcO). The crystal 402 was obtained in 70% (2.35g). 1 H-NMR (300.07 MHz; DMSO-d6) δ (ppm): 9.65 (s, 1H), 7.97 (d, J=7.9, 2H), 7.53 (d, J=7.9, 2H), 7.22 (d, J=7.5, 1H), 7.03 (dd, J=7.0, 7.5, 1H), 6.83 (d, J=7.9, 1H), 6.77 (d, J=8.8, 2H), 6.65 (dd, J=7.5, 7.0,1H), 6.57 (d, J=8.8, 2H), 4.93 (bs, 2H), 4.36 (d, J=5.7, 2H), 3.75 (m, 4H), 2.93 (m, 4H). LRMS: calc 402.49; found: 403.4.

Scheme 60

Example 283a

Step 1. 4-[(3,4-Dimethoxyphenylamino)-methyl]-benzoic acid (424a)

[0374] In a 50 ml flask, a mixture of 4-aminoveratrole (1.53 g, 10 mmol), 4-formyl-benzoic acid (1.50 g, 10 mmol), dibutyltin dichloride (304 mg, 1 mmol), phenylsilane (2.47 ml, 20 mmol) in anhydrous THF (10 mL) and DMA (10 ml) was stirred overnight. at room temperature. After solvents removal, the crude residue was dissolved in ethyl acetate (100 ml) and then washed with saturated aqueous solution of NaHCO₃ (50 ml x 3) . The combined aqueous layers were acidified with 6% of NaHSO₄ to pH = 4. The resulting white suspension was filtrated and then the filter cake was washed with water (5 ml x 3). The cake was dried over freeze dryer to afford acid (1.92 g, 67 %) white solid product. LRMS = 288 (MH) $^+$.

Step 2. N-(2-Aminophenyl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide (424b)

[0375] In a 150 ml flask, a mixture of acid (1.92 g, 6.69 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 3.26 g, 7.37 mmol), triethylamine (1.87 ml, 13.4 mmol), o-phenylenediamine (1.30g, 12.02 mmol) in methylenechloride (67 ml) was stirred at rt for 2 h. After solvents removal, the crude residue was dissolved in EtOAc (100 ml) and then washed with NaHCO₃ saturated solution and brine 50 ml. The combined organic layers were dried over Na₂SO₄ and the filtrate was concentrated to dryness. The crude material was submitted to a chromatographic purification (column silica, 55%-70 % EtOAc in 1% Et₃N of hexanes) and then the all interested fractions were concentrated to dryness. The residue was suspended in minimum

quantities of ethyl acetate and then filtered to afford final product (1.49 g, 59 %). 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.5, 7.5 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH₂), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).

Example 283b

Step 1: N-(4-Aminothiophen-3-yl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide:

[0376] Acid 424a (1040 mg; 3.62 mmol); 3,4-diaminothiophene dihydrochloride (1017 mg; 5.44 mmol; 1.50 eq.) and BOP (1770 mg; 4.0 mmol; 1.1 eq.) were suspended in MeCN, treated with triethylamine (4 mL; 29 mmol) and stirred for 18h at room temperature; concentrated and purified by chromatographic column on silica gel (elution 50% EtOAc in DCM) to render 527 mg (1.37 mmol; 38 % yield) of compound 424c which was 90% pure. 1H-NMR (300.07 MHz; DMS0-d6) δ (ppm): 8.56 (s, 1H), 7.78 (d, J=7.9 Hz, 2H), 7.43 (d, J = 3.5 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 3.5 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 6.13 (dd, J = 2.6, 8.3 Hz, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). LRMS: calc: 383.4642; found: 384.2 (M+H); 406.2 (M+Na) and 192.6 (M+2H)/2.

Scheme 61

Step 1: Methyl-(5-nitrobenzothiazol-2-yl)-amine (456a)

[0377] A mixture of 2-fluoro-5-nitroaniline (861 mg; 5.52 mmol; 1.02 eq); Im_2CS (960.3 mg; 5.39 mmol) and dry K_2CO_3 (1.45g) was suspended in dry DME (10 mL) and stirred under nitrogen for 90 min at room temperature. The yellow suspension was made fluid by diluting with DME (10 mL) followed by addition of 40% MeNH₂ in water (4.0 mL; 46.5 mmol; 8.6 eq). The system was heated up

to 65C and stirred at this temperature for 3.5 h, cooled down, diluted with ethyl acetate and washed with saturated NaCl (X2). After conventional work-up procedures, the dark crude mixture was purified through chromatographic column on silica gel (elution 50% EtOAc in hexane, then 5% MeOH in DCM), to afford 836.8 mg (4.0 mmol; 72% yield) of compound **456a**.

Step 2: N-Methyl-benzothjazole-2,5-diamine (456b)

[0378] A mixture of nitro compound 456a (593 mg; 2.83 mmol); $SnCl_2$ (4.02 g; 20.8 mmol; 7.35 eq) and NH_4OAc (4.5g) was suspended in THF:MeOH: $H_2O=1:1:1$ (60 mL) and stirred at 70°C for 2 h, cooled down, diluted with ethyl acetate and successively washed with saturated $NaHCO_3$ and brine; dried (MgSO₄) filtered and concentrated. The residue (443 mg; 2.43 mmol; 87%) showed consistent spectrum and suitable purity degree for synthetic purposes, therefore was submitted to the next step without further purification.

Step 3: 4-[(2-Methylaminobenzothiazol-5-Ylamino)-Methyl]-Benzoic Acid (456c)

[0379] A solution of aniline 456b (509 mg; 2.8 mmol); 4-formylbenzoic acid (426 mg; 2.8 mmol) and Bu_2SnCl_2 (198 mg; 0.65 mmol; 23% mol) in DME (14 mL) was stirred at room temperature for 3 min and treated with neat PhSiH₃ (0.6 mL; 4.7 mmol; 1.7 mmol) and allowed to react for 18h. After quenching the excess of silane with MeOH, the mixture was concentrated and purified by chromatographic column on silica gel (elution 5% MeOH in DCM) to give 729 mg (2.54 mmol; 91% yield) of acid 456c.

Step 4: N(2-Aminophenyl)-4- $\{(2-\text{methylaminobenzothiazol-5-ylamino})$ -methyll-benzamide (456) [0380] A mixture of acid 456c (729 mg; 2.54 mmol), 1,2-phenylenediamine (376 mg; 3.47 mmol; 1.36 eq) and BOP (1.43 g; 3.23 mmol; 1.27 eq) was dissolved in acetonitrile (15 mL), treated with triethylamine (3mL) and stirred overnight. The reaction mixture was quenched with methanol, concentrated and purified by chromatographic column on silica gel (40% EtOAc in DCM) and the obtained material crystallized from DCM to give 358 mg (0.88 mmol; 35 % yield) of pure compound 456. 1 H-NMR (300 MHz; DMSO-d6) 8 (ppm): 9.57 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.76 4.87 (bs, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.13 (dd, J = 1.8, 8.3 Hz, 1H), 6.27 (t, J = 5.7 Hz, 1H), 4.87 (bs, 2H), 4.36 (d, J = 5.7 Hz, 2H), 2.85 (d, J = 4.8 Hz, 3H). LRMS: calc: 403.5008, found: 404.2 (M+NH) and 202.6 (M+2H)/2.

Scheme 62

Example 235

Step 1: Methyl-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoate (376a)

[0381] To a solution 5-methoxy-2-thiobenzimidazole (2.00 g, 11.1 mmol of in anhydrous DMF (40 ml) was added methy-4-(bromomethyl)-benzoate (2.54 g, 11.1 mmol). The reaction mixture was stirred 16 h at room temperature. The DMF was evaporated and the residue was triturated in ethyl acetate during 30 min and then filtered and dried. The desired compound was isolated as the HBr salt: 98% yield, (4.44 g). 1 H NMR: (DMSO) δ (ppm): 7.90 (d, J = 8.8 Hz, 2H), 7.56-7.52 (m, 3H), 7.09 (d, J = 2.2 Hz, 1H), 7.01 (dd, J = 8.8 , 2.2 Hz, 1H), 4.73 (s, 2H), 3.82 (s, 6H). MS: (calc.) 328.1, (obt.), 329.2 (MH)+.

Step 2: 4-(5-Methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid (376b)

[0382] A solution of LiOH.H2O (1.02 g, 24.4 mmol) in water (15 ml) was added to a suspension of 376a (3.99 g, 9.75 mmol of in THF (10 ml). The reaction mixture was stirred 16 h at room temperature. The reaction mixture was acidified with a solution of HCl 1 M to pH 4. The desired product was triturated 20 min. at 0°C and then filtered and dried. Compound 376b was obtained as a white powder (100% yield, 3.05 g). 1 H NMR: (DMSO) δ (ppm): 12.85 (bs, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.8 , 2.2 Hz, 1H), 4.60 (s, 2H), 3.82 (s, 3 H). MS: (calc.) 314.1, (obt.), 315.1 (MH)+.

Step 3: N(2-Amino-phenyl)-4(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzamide (376)

[0383] Following the procedure described in Example 1 step 5 but substituting 4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid 2 for 7 the title compound 376 was obtained as a white powder.: 36% yield (933 mg). 1 H NMR: (DMSO) δ (ppm): 12.42 (bs, 1H), 9.57 (bs, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.98-6.93 (m, 2H), 6.77-6.55 (m, 2H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.87 (s, 2H), 4.59 (s, 2H), 3.77 (s, 3 H). MS: (calc.) 404.1, (obt.), 405.4 (MH)+.

Examples 180-328

[0384] Examples 180 to 327 (compounds 320 - 468) were prepared using the same procedure as described for compound 126 to 319 in Example 85 to 179 (scheme 11 to 58).

Examples 329-344

[0385] Examples 329 to 344 (compounds 470 - 485) were prepared using the same procedure as described for compound 8 to 224 in Example 1 to 143 (scheme 1 to 32).

Scheme 63

Example 345

Step 1: Methyl 3-(4-bromo-phenyl)-acrylic ester (486)

[0386] To a solution of anhydrous iPr_2NH (758 μl, 5.40 mmol) in anhydrous THF (25 ml) stirred at 0°C under nitrogen , was slowly added a solution of nBuLi (2.22 ml, 5.54 mmol, 2.5 M in hexane). After 30 min, LDA was cooled to -78°C and anhydrous methyl acetate (430 Ω l, 5.40 mmol) was added dropewise. After 30 min, a solution of 4-bromobenzaldehyde (500 mg, 2.70 mmol) in anhydrous THF (10 ml) was slowly added. After 30 min, a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (569 mg, 3.24 mmol) in anhydrous THF (15 ml) was added. Then, the temperature was allowed to warm up to room temperature overnight. A suspension appeared. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with H_2O and brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt/hexane: 10/90) to give the title product **486** (394 mg, 1.9 mmol, 61% yield) as a coloriess crystalline solid. 1H NMR (300 MHz, CDCl₃) δ (ppm): 7.63 (d, J = 16.2 Hz, IH), AB system ($\delta_A = 7.53$, $\delta_B = 7.39$, J = 8.4 Hz, IH), 6.43 (d, I = 15.8 Hz, IH), 3.82 (s, 3H).

Step 2: Methyl 3-[4-(3,4,5-trimethoxy-phenylamino)-phenyll-acrylic ester (487)

[0387] A mixture of Cs_2CO_3 (378 mg, 1.16 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), (rac)-BINAP (23 mg, 0.037 mmol), was purged with nitrogen for 10 min. 486 (200 mg, 0.83 mmol), 3,4,5-trimethoxyaniline (182 mg, 0.99 mmol), and anhydrous toluene (5 ml) were added, respectively. The reaction mixture was heated to $100^{\circ}C$ under nitrogen for 24 h. Then, it was allowed to cool to room temperature, diluted with AcOEt, and successively washed with a saturated aqueous solution NaHCO₃, H₂O, sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the title compound 487 (280 mg, 0.82 mmol, 98% yield) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.64 (d, J = 16.2 Hz, 1H), 7.43 (bd, J = 7.9 Hz, 2H), 7.12-6.86 (m, 2H), 6.60-6.20 (m, 3H, included at 6.29, d, J = 15.8 Hz), 3.84 (s, 9H), 3.80 (s, 3H).

Step 3: N(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylamide (488)

[O388] The title compound 488 was obtained from 487 in 2 steps following the same procedure as Example 1, steps 4 and 5. 1 H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.29 (s, 1H), 8.48 (s, 1H), 7.60-7.42 (m, 3H), 7.38 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.94 (t, J = 7.5 Hz, 1H), 6.78

(d, J = 7.9 Hz, 1H), 6.71 (d, J = 15.8 Hz, 1H), 6.61 (t, J = 7.1 Hz, 1H), 6.47 (s, 2H), 4.97 (s, 2H), 3.79 (s, 6H), 3.66 (s, 3H).

Scheme 64

Example 346

Step 1: 3-(4-Formyl-3-methoxy-phenyl)-acrylic acid tert-butyl ester 489

[0389] Following the procedure described in Example 53, step 1, but substituting 4-hydroxy-2-methoxy-benzaldehyde for 84, followed by Example 42, step 2, but substituting the previous compound for 42, the title compound 489 was obtained in 29% yield. LRMS = calc: 262, found: 263.2 (M+H⁺).

Step 2: 3-{3-Methoxy-4-{(3,4,5-trimethoxy-phenylamino}-methyl}-phenyl}-acrylic acid tert-butyl ester 490

[0390] Following the procedure described in Example 144, step 3, but substituting 489 for 4-formylbenzaldehyde, the title compound 490 was obtained in 69% yield. LRMS = calc: 429, found: 430.5 (M+H⁺).

Step 3: N(2-Amino-phenyl)-3-{3-methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide 491

[0391] Following the procedure described in Example 42, step 3, 4, but substituting 490 for 46, the title compound 491 was obtained in 67% yield. ¹H NMR (CDCl₃), δ (ppm): 8.08 (s, 1H), 7.74 (d, J = 15.4 Hz, 1H), 7.30 (m, 1H), 7.06 (m, 3H); 6.80 (m, 3H), 6.70 (d, J = 15.4 Hz, 1H), 5.98 (s, 2H), 4.40 (s, 2H); 4.12 (bs, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.77 (s, 6H).

Scheme 65

Example 436

Step 1: Methyl-5-methyl-benzofuran-2-carboxylate (583)

[0392] A stirring suspension of 5-methylsalicylaldehyde (1.0 mg, 7.5 mmol), K_2CO_3 (1.55 g, 11.0 mmol), and Bu_4NBr (322 mg, 1 mmol) in toluene (30ml) was treated with dimethylbromomalo-nate (1.06 ml, 8.0 mmol). The suspension was heated to reflux with a Dean-Stark trap for 20 h. The brown

suspension was cooled to 25° C and concentrated in vacuo. The residue was taken in DCM and filtered. The filtrate was washed with H_2O , 1N NaOH and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by column chromatography (10% ethyl acetate/hexane) to afford the title compound 583 (600mg, 42% yield). LRMS: 190.2 (Calc.); 191.1 (found).

Step 2: Methyl-5-bromomethyl-benzofuran-2-carboxylate (585)

[0393] A mixture of 583 (500 mg, 2.63 mmol), N-bromosuccinimide (561 mg, 3.15 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (Vazo) (63 mg, 0.26 mmol) in 15 ml of CCl₄ was heated overnight under reflux. The mixture was cooled to room temperature, quenched by adding water and extracted with DCM. The organic layer was washed with brine and dried over MgSO₄, filtered and concentrated. The crude residue was purified by column chromatography (30% ethyl acetate/hexane) to afford the title compound 585 (680mg, 96% yield). ¹H NMR: (CDCl₃) δ (ppm): 7.79 (s, 1H), 7.70-7.52 (m, 3H), 4.69 (s, 2H), 4.06 (s, 3H), 3.72 (s, 2H). LRMS: 268.2 (Calc.); 269.1 (found).

Step 3: Methyl-5-{(3,4-dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylate (586)

[0394] Following the procedure described in Example 47, step 2, but substituting 585 for 63, the title compound 586 was obtained in 40% yield. LRMS: 341 (Calc.); 342.3 (found).

Step 4: 5-[(3,4-Dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (587)

[0395] Following the procedure described in Example 1, steps 4,5, but substituting **585** for **6**, the title compound **587** was obtained in 29% yield. 1 H NMR: (DMSO) δ (ppm): 9.83 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 5.5 Hz, 1H), 4.93 (s, 2H), 4.31 (d, J = 5.5 Hz, 1H), 2.82 (s, 3H), 2.76 (s, 3H). LRMS: 417.46 (Calc.); 418.4 (found).

Example 437

Step 1: Methyl-5-nitro-benzo[b]thiophene-2-carboxylate (584)

[0396] A stirring suspension of 5-nitro-2-chloro-benzaldehyde (4.0 g, 21.6 mmol) in DMF (40 ml) at 5°C was treated with K_2CO_3 (3.52 g, 25.5 mmol) followed by methylglycolate (1.93 ml, 21.6 mmol). The resulting solution was warmed to 25°C and stirred for 20h. The solution was then poured into 250ml of ice H_2O and the white precipitate that formed was collected by filtration. Crystallization

from EtOAc afforded fine pale orange needles of **584** (3.54 g, 69%). LRMS: 237.0 (Calc.); 238.1 (found). 1 H NMR: (DMSO) δ (ppm): 9.00 (d, J = 2.2 Hz, 1H), 8.45 (s, 1H), 8.39-8.30 (m, 2H), 3.93 (s, 3H).

Step 2: Methyl-5-amino-benzo[b]thiophene-2-carboxylate (588)

[0397] A suspension of 584 (3.52 g, 14.8 mmol) in methanol (100 ml) was treated with Fe powder (6.63 g, 118.7 mmol). The resulting suspension was heated to reflux, and 12M HCl (8.5 ml) was slowly added over 15 min. The resulting green dark suspension was refluxed for an additional 3 h, then cooled and concentrated. The residue was taken up in EtOAc and washed with saturated aqueous NaHCO₃, then brine, dried over MgSO₄, filtered and concentrated to afford (2.57 g, 84%). 1 H NMR: (DMSO) δ (ppm): 7.92 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 1.8, 8.4 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H). LRMS: 207.0 (Calc.); 208.1 (found).

Step 3: Methyl-5-(3,4,5-trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylate (589)

[0398] Following the procedure described in Example 144, step 3, but substituting 588 for 226, the title compound 589 was obtained in 68% yield. (DMSO) δ (ppm): 7.94 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.73 (s, 2H), 6.41 (t, J = 5.7 Hz, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 6H), 3.62 (s, 3H). LRMS: 387.1 (Calc.); 388.3 (found).

Step 4: 5-(3,4,5-Trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (590)

[0399] Following the procedure described in Example 1, steps 4,5, but substituting **589** for **6**, the title compound **590** was obtained in % yield NMR: (DMSO) δ (ppm): 7.79 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.00-6.95 (m, 2H), 6.74 (s, 2H), 4.32 (s, 2H), 3.80 (s, 6H), 3.73 (s, 3H).

Examples 347-425

[0393] Examples 347 to 425 (compounds 492-570) were prepared using the same procedure as described for compound 44 to 491 in Example 40 to 346 (scheme 3 to 64).

Assay Example 1

Inhibition of Histone Deacetylase Enzymatic Activity

1. Human HDAC-1

[0394] HDAC inhibitors were screened against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system. For deacetylase assays, 20,000 cpm of the [³H]-metabolically labeled acetylated histone substrate (M. Yoshida *et al., J. Biol. Chem.* **265(28):** 17174-17179 (1990)) was incubated with 30 μg of the cloned recombinant hHDAC-1 for 10 minutes at 37 °C. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCI (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [³H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 °C for 30 minutes prior to initiation of the enzymatic assay. IC₅₀ values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition. IC₅₀ values for representative compounds are presented in the third column of Table 5.

2. MTT Assay

[0395] HCT116 cells (2000/well) were plated into 96-well tissue culture plates one day before compound treatment. Compounds at various concentrations were added to the cells. The cells were incubated for 72 hours at 37°C in 5% CO₂ incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before one volume of solubilization buffer (50% N,N-dimethylformamide, 20% SDS, pH 4.7) was added onto the cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM using an MR700 plate reader (Dynatech Laboratories Inc.). OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of that of solvent treated cells is determined as MTT IC₅₀. IC₅₀ values for representative compounds are presented in the fourth column of Table 5.

3. Histone H4 acetylation in whole cells by immunoblots

[0396] T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 h. Histones were extracted from the cells after the culture period as described by M. Yoshida et al. (J. Biol. Chem. 265(28): 17174-17179 (1990)). 20 g of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H-4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry. Representative data are presented in the fifth column of Table 5. Data are presented as the concentration effective for reducing the acetylated H-4 signal by 50% (EC₅₀).

Table 5a: Inhibition of Histone Deacetylase

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
8		0.4	0.5	1
9	NH 2 N N N N N N N N N N N N N N N N N N N	2	0.7	5
10	NH2 NH2 NH2 NH2 NH2 NH2	2	0.6	1
11	NHZ NHZ	2	0.6	2
12	NH ₂	2	2	5

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
14	NH2 N N N N N NH2	0.3	1	5
15	NH ₂	0.5	0.2	3
16	H ₂ N NH	1	0.4	1
17	H ₃ C H ₃ H H ₂ N H H ₂ N N H H ₂ N N N H H ₂ N N N N N N N N N N N N N N N N N N N	0.9	1	2
18	HN CH ₂ N N N N N N N N N N N N N N N N N N N	0.8	0.6	3
18b		0.6	5	10
19	LI L	0.9	1	1
20		0.5	0.3	1

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
21	OMe NH ₂ MeO NH ₂ N N N N N N N N N N N N N N N N N N N	4	4	25
22	NH ₂ N N N N N N N N N N N N N N N N N N N	3	0.8	1
23	NH ₂	2	0.7	1
24	F 2-T	3	0.6	1
25	HN N N H NH2	0.8	0.3	. 5
26		0.5	2	na
27	HN N N N NH2	0.4	2	na
28	NH2 NH2 NH2	2	0.5	1

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
29	NH ₂ N N N N N N N N N N N N N N N N N N N	2	2	1
30		1	3	1
83	NH ₂	3	5	5

(na = not available; $99 = >25 \mu M$)

Table 5b

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
135	204	NH ₂ N N N N N N N N N N N N N N N N N N N	4	na	5
136	207	NH ₂ N N N N N N N N N N N N N N N N N N N	0.4	0.6	2
137	210		3	0.9	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
138	212	OMe N N N N N N N N N N N N N N N N N N N	3	1	1
139	214	OMB N N N N N N N N N N N N N N N N N N N	3	0.9	1
140	216	NH ₂ N N N N N N N N N N N N N N N N N N N	0.5	0.4	2
141	218	Me Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	0.1	0.5	na
142	220	NH ₂ N N N N N N N N N N N N N N N N N N N	7	6	na
143a	223	NH ₂ N NH ₂ N NH ₂ N NH ₂	11	2	na
143b	224	NH2 N NH2	5	3	na

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
329	470	NH ₂	2	0.7	3
330	471	NH ₂	. 0.4	1	3
331	472		3	1	1
332	473	HN CH ₃ N H N NH ₂ N H N N NH ₂ N H N	4	3	na
333	474	HN O CH ₃ NH N	3	1	1
334	475	CI Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	0.6	2	na
335	476	MeO N N N N N N N N N N N N N N N N N N N	2	1	2

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
336	477	CI HN NH2	1	0.7	na
337	478	MeO HN N H N N H 2	3	0.7	na
338	479	OMe HN N N N N N N N N N N N N N N N N N N	0.4	0.6	na
339	480	HN N N NH2	0.8	0.5	na .
340	481	HN N NH2	6	0.7	na
341	482	HN N N N N N N N N N N N N N N N N N N	0.1	0.7	na
342	483	Me N N N N N N N N N N N N N	4	na	na

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
343	484	NH ₂ N N N N N N N N N N N N N N N N N N N	2	0.3	na
344	485	NH2 NH NH2	0.4	3	na

(na=nonavailable)

Table 5c

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
51	Me O NH	22	4	na
55b	O NH NH ₂	3	8	3
59	MeO N NH2 MeO OMe O	12	22	na
61b	MeO NH NH2	7	12	na
65	NH ₂	4	37	na

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
71	D NH2	10	44	na
72	MeO NH NH ₂	16	21	na
88	NH NH ₂	na	>39	na
90	NH NH ₂	10	5	5
91	N H NH2	4	7	5
92	F NH NH2	5	2	3
93	NH NH ₂	3	1	5
94	NH NH ₂	3	2	5
95	MeO NH NH2	3	2	10

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
96	Me. NH NH2	4	3	25
97	NA NH2	10 ·	12	na
98	OCF 3	0.4	2	15
99	CF ₃ O NH NH ₂	2	5	10
100	F NH NH 2	4	3	5
101	ONH NH2	3	0.9	5
102	O NH NH2	20	6	na
104	ST HS O ST HS	10	9	5
105	ON NH2	16	14	na

Cpd	Structure	HumanHDAC-1 IC₅₀(μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
106	Me O NH 2	2	2	1
107	Me O NH NH2 Me O OMe O	15	17	па
108	MeO NH ₂ NH ₂ NH ₂	3	5	5
109	MeO N NH NH2	5	8	15
110	S NH NH ₂	3	999 .	na
111	N NH2	10	2	99
112	NH NH2	2	5	5
113	O ₂ N N N N NH ₂		0.3	5

Cpd	Structure	HumanHDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4Ac(T24) EC ₅₀ (μM)
114	Me O NH NH2	25	0.5	99 .
115	N N N N N N N N N N N N N N N N N N N	15	9	na
116	MeO OMe	4	2	5
117	NH NH ₂	7	3	na
118	MeO NH2	11	8	na

Table 5d

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
338	481	MeO H NH2 MeO OMe	22	10	-
339	484	MeO NH NH ₂	20	12	•

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
347	492	H ₃ C'O N N NH ₂	4	9	10
348	493	CI N NH2	4	5	-
349	494	H ₃ C O CH ₃	3	4	-
350	495	O ₂ N H NH ₂	4	7	-
351	496	F F HN H ₂ N	8	13	-
352	497	H ₃ C O N NH ₂ H ₃ C O O O O O O O O O O O O O O O O O O O	15	6	-
353	498	CH ₃ N N NH ₂	>25	-	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
354	499	H ₃ C O CH ₃	>25	2	>25
355	500	H ₃ C-O O H ₃ C' H ₃ C-O H ₂ N	23	37	-
356	501	CH ₃ O HN H ₂ N	4	10	-
357	502	H ₃ C H ₂ N	3	>25	-
358	503	O N-O HN-O H ₂ N	5	>25	· <u>-</u>
359	504	F ₃ CO H NH ₂	5	>25	-
360	505	NH O HN H ₂ N	3	6	-
361	506	OCF ₃	15	11	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
362	507	H H NH ₂	17	10	
363	508	OMe NH ₂	22	11	<u>-</u>
364	509	O N NH2	17	11	-
365	510	H ₃ C H ₃ NH ₂	6	5	-
366	511	H NH2	4	>25	
367	512	MeO HO NH2	3	3	5
371	516	Br NH2	15	15	-
372	517	MeO HN O HN H2N	6	5	-
373	518	MeO H ₃ C O O HN HN H ₂ N	4	2	5

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(µM)
374	519	N NH2	99	6	-
375	520	NH ₂ H NH ₂	5	3	-
376	521	NH NH2	5	2	10
377	522	S N N N N N N N N N N N N N N N N N N N	17	30	-
378	523	MeO NH NH ₂	8	6	10
379	524 ·	12 T T T T T T T T T T T T T T T T T T T	3	2	3
380	525	ONH NH2	3	4	5
381	526	NH NH ₂	2	0.8	1
382	527	NH NH₂	4	<u>.</u> 3	<u>.</u> .

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
383	528	NH NH ₂	20	32	-
384	529	NH NH ₂	5	17	-
385	530	HO NH₂	8	9	-
386	531	NH NH ₂	3	2	20
387	532	NH NH ₂	3	5	
388	533	NHAc NH2	5	11	-
389	534	O ₂ N CF ₃	3	5	-
390	535	CI NH NH ₂	4	6	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
391	536	MeO NH NH ₂	18	9	-
392	537	MeO OMe NH NH ₂	11	2	>25
393	538	NH NH ₂	4	12	-
394	539	O ₂ S NH ₂	2	10	
395	540	MeO NH NH ₂	10	10	
396	541	H ₃ C ₀ NH NH ₂	4	12	-
397	542	CH3 HN NHN	2	5	4
398	543	NH N	15	>25	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
399	544	N-N NH ₂	17	45	
400	545	Br NH ₂	2	12	
401	546	H NH NH ₂	3	10	-
402	547	NH NH ₂	4	8	-
403	548	NH NH ₂	3	9	-
404	549	NH NH ₂	4	19	<u>-</u>
405	550	O ₂ N NH ₂	4	15	-
406	551	NH ₂	24	9	-
407	552	CI NH NH2	4	22	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
408	553	O DH NH2	4	12	
409	554	PH NH ₂	15	12	-
410	555	NH NH ₂	14	7	-
411	556	NH NH ₂	1	0.4	15
412	557	O NH NH ₂	4	6	-
413	558		7	10	
414	559	P NH2	. 4	11	-
415	560	MeO OMe NH ₂	21	6	-
416	561	H ₃ C ₂ O H ₃ C ₂ O H ₃ C ₃ O H ₃ C ₄ O H ₃ C ₅ O H ₃ C H ₃	>25	>25	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
417	562	OMe H NH NH2	5	5	<u>.</u> .
418	563	OMe OMe OMe HN H NH NH ₂	24	6	-
419	564	H ₃ C O N H ₂ NH ₂ NH ₂	>25	>25	-
420	565	H ₃ C. _S	5	17	-
421	566	F F N NH2	3	16	-
422	567	H ₃ C-O-H ₃	13	3	-
423	568	H ₃ C O O O O O O O O O O O O O O O O O O O	>25	39	-
424	569	H ₃ C NH NH ₂	18	6	-

Ex.	Cpd	Structure	HDAC-1 IC50(μM)	MTT(HCT116) IC50(μM)	H4Ac(T24) EC50(μM)
425	570	H ₃ C-O	6	0.6	2

Table 5e

Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
87	NH NH ₂	2	1 .	5
126	N S N N NH ₂	0.3	0.2	1
128	CN N S S S S S S S S S S S S S S S S S S	1.	0.3	5
131	H ₂ N	0.3	0.9	2
139	N S N N NH2	3	3	5
141	MeO H H ₂ N	7	10	na
149		1	5	5

Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
152	H H ₂ N	0.3	· 11	na ·
154	N NH2	0.3	0.4	<1
155	N N N N N N N N N N N N N N N N N N N	0.4	0.4	1
157	N N N N N N N N N N N N N N N N N N N	2	0.6	1
158	NH2 NH2 NH0	0.4	0.2	1
164	MeO H NH NH 2	3	2	.3
165	H ₃ C — H ₃ C H ₃ C	9	4	25
166	MeO H H ₂ N	2	5	5
167	MeO H NH2	4	0.5	2
168	MeO NH2	3	0.8	2

Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT(HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
169	MeO NH NH NH2	0.3	0.7	1
171	NH NH ₂	8	3	25
172	N ₂ S N _H N _{H₂}	0.4	1	3
174	F NH ₂	4	0.4	5
· 175	F N N NH2	4	0.5	3
176	MeO N N NH 2	5	1	3
177	N.N.S. N.H.2	1	0.4	. 1

Table 5f

	T		T		
Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) H4 Ac (T24)
117	179	H NH2	1	0.3	1
118	180	H ₂ C H ₃ C H NH ₂	3	2	5
119	181	NH ₂	0.5	0.4	1
122	186	H NH ₂	2	2	2
123	187	N H NH ₂	2	5	2
125	189	MeO H NH ₂	3	2	5
126	190	MeO H NH ₂	3	1	>5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
127	192	NH NH ₂	2	1	3
128	193	H ₂ C H ₃	4	16	
129	194	H ₃ C _O O H ₂ N H ₂ N	3	11	
130	195	H ₃ C CH ₃	7	9	
131	196	NH ₂	4	3	
132	198	H ₃ C, CH ₃ H ₃ C, Si H ₃ C, NH ₂	24	14	
133	199	HC NH ₂	7	9	

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
134	201	CI NH2	11	5	
144	228		3	0.3	1
145	231	CH ₃ S NH O H ₂ N	4	1	3 ·
146	233	H ₃ C ₁ O	0.9	0.3	1
147	236	ON S H NH2	5	6	
148	238		3	6	
149	240		1.8	10	
150	243	NH ₂ CI N N O-CH ₃	2	0.8	1
151	247	H ₂ C N N N N N N N N N N N N N N N N N N N	3	0.6	2

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
152	249	E E	4	1	2
153	252	NH ₂	8	1	2
154	255	S N NH2	2	0.8	1
155	257	S N N N N N N N N N N N N N N N N N N N	0.4	0.4	1
156	259	H ₃ C S N NH ₂	3	0.3	1
157	262		0.5	0.3	. 1
158	265		2	2	3
159	266	NH2	0.4	0.9	. 2
160	269	H ₃ C N NH ₂	9	4	
161	270		4	1	. 5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
162	272	NH ₂	2	0.6	<1
163	275	OH NH2	4	0.9	2
164	277	CH ₃ N. CH ₃ O	4	0.3	1
165	281	NC — S — CH ₃	0.5	0.6	1
166	284	H ₃ C $\stackrel{\circ}{\swarrow}_N$ $\stackrel{\circ}{\bigvee}$ $\stackrel{\circ}{\bigvee}_N$ $\stackrel{\circ}{\bigvee}_N$ $\stackrel{\circ}{\bigvee}_N$ $\stackrel{\circ}{\bigvee}_N$	3	5	
167	286	H ₃ C — N-N H NH ₂	5	2	
168	289	H ₂ COCH ₃ CH ₃ NH ₂ NH ₂	17	5	
169	290	CH ₃ O-CH ₃ H ₂ N H ₃ C	11	3	
170	296	O N NH2 H ₃ C H ₃ C H ₃ C	20	7	
171	297	MeO N NH2	7	0.4	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
172	301	H ₃ C-O N N NH ₂	3	3	
173	305	H ₃ C-O N N NH ₂	4	2	
174	311	MeO S S H OH	0.9	0.7	1
178	317	SMe HN O NH2 NHO OMe	2	0.3	1
179	319	NH ₂	4	8	
180	320	CI N N NH2	2		1
181	321	CI—ON NH2	0.5	0.3	5
182	322	Br — S	0.7	0.4	2
183	323	MeO OMe H NH2	1	0.6	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
184	325	N S NH ₂	0.3	1	2
185	326	N S NH ₂	1	1	3
186	327	NH S NH NH ₂	2	5	3
187	328	ON NH2	17	10	
189	330	O NH NH2N N N CH3	3	2	1
190	331	NH H ₂ N N HCI	4	10	
191	332	NH CI NH N	0.4	1	5
192	333	NH CI NH N	2	0.1	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
193	334	H ₂ N HN HN HN	8	0.2	1
195	336		1	0.4	<1
196	337	O H NH2	. 3	0.6	1
197	338	MeO N NH ₂	2	0.5	3
198	339	F NH2	4	3	
199	340	H ₃ C CH ₃	2	1	1
200	341		4	1	3
201	342	Br CH ₃ NH ₂	3	0.4	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
202	343	S NH ₂	0.5	0.3	1.
203	344	Br NH ₂	0.5	0.2	1
204	345	Meo O	0.4	0.8	1
205	346	Br N N N N N N N N N N N N N N N N N N N	3	0.5	<1
206	347	Br N-N H2N H2N N N N N N N N N N N N N N N N	2	0.6	2
207	348		2	0.3	1
208	349	E N H NH2	13	1	3
209	350	F F N H ₂ N	2	1	5
211	352	O-N N NH2	16	9	

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
212	353	H ₃ C N NH ₂	3	10	
213	354		15	5	·
214	355		25	10	
215	356	H ₃ C N NH ₂	5	2	
216	357	O NH ₂	4	0.4	2
217	358	N NH ₂	3	1	2
218	359	N S HN NH2 O CH3	2	0.3	1
219	360	CH ₃ NC NC N N N N N N N N N N N N N N N N	5	0.2	1
220	361	NC S H NH ₂	2	0.5	1
221	362		2	0.7	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
222	363	NH ₂	1	0.3	3
223	364	O N N NH ₂	4	0.6	
224	365	OH H ₂ N	3	0.6	3
225	366	H NH ₂	14	10	
226	367	MeO NH ₂ N	6	2	5
230	371	OMe OMe HN O N N H N N	4	0.5	2
231	372	HN O H2N H	2	0.2	1
232	373	HN O N H	4	0.4	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (µM)
233	374	H ₂ C CH ₃ H ₂ N	2.5	0.3	1
234	375	O NH NH ₂ H ₂ N	3	4	25
235	376	O H,N	3	0.1	1
236	377	NH NH	4	2	3
237	378	H ₃ C N S NH NH ₂	2	0.7	2
238	379	F F N S NH NH ₂	2	0.6	15.
239	380	NH ₂ NH ₂ NH ₂ NH ₂ NH ₂	6	8	

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
240	381	S O NH	2	1	2
241	382	H ₃ C N NH ₂	3	1	3
242	383	H ₃ C H ₃ C NH NH NH ₂	2	0.5	2
243	384	H ₃ C NH ₂	3	2	5
244	385	H ₃ C ₀ N H ₂ N	3 .	1	2
245	386	CH ₃ HN O HN O H ₂ N	3	1	1
246	387	H ₃ C-O NH	· 2	1	1
247	388	H ₃ C-O H ₂ N H ₂ N	3	0.4	5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
248	389	NH ₂	3	0.2	1
249	390	H ₃ C 0 N H NH ₂	2	0.8	5
250	391	NH NH ₂	1	0.9	3
251	392	H,C-0 H,NH NH2	4	1	1
252	393	H ₂ C ⁻⁰ NH NH ₂	4	0.6	1
253	394	H ₃ C-O NH- NH-	4	2	25
254	395	H ₃ C-O	2	1	5
255	396	NH ₂	2	0.7	5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
256	397	CH ₃ O CH ₃ O CH ₃ O HN H ₂ N	1	0.6	4
258	399	NH NH O	14	9	
259	400	ON NH2	8	0.3	2
260	401	H ₃ C NH O H ₂ N	6	0.3	2
261	402		14	0.4	1
262	403	H ₃ C H ₂ N H ₂ N	1	0.2	1
263	404	H ₃ C CH ₃ NH HN HN H ₂ N	3	0.6	5
264	405	H ₃ C ₀ H _N H _N H _N NH ₂	5	1	5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
265	406	HO O H NH2 H ₃ C O CH ₃	3	11	
266	407	H ₂ C H ₃	3	2	
267	408	N N NH ₂	4	2	
268	409	CH ₃ H NH ₂	3	1	9999
269	410	CH ₃ H NH ₂	0.9	0.1	· >5
270	411		2		1
271	412	MeO H H NH2	3	2	3
272	413	P N NH2	2	2	3

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
273	414	MeO NH ₂	3	1	1'
274	415	P NH2	3	1	3
275	416	TH NH	3	0.6	1
276	417	NH ₂	3	1	1
277	418	CI N H NH ₂	3	0.9	2
278	419		2	1	5
279	420	CI N H NH2	3	0.7	1
280	421	H ₃ C·ON NH ₂	4	0.6	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
281	422	E-LO H NH	<0.05	0.9	5
282	423	# # # # # # # # # # # # # # # # # # #	0.5	1	3
283a	424b	H NH ₂ MeO OMe	2	0.4	1
283b	424c	MeO OMe	3	0.8	3
284	425	OCF ₃	2	0.6	5
285	426	F ₃ CO N NH ₂	2	1	10
286	427	MeO NH NH2	0.6	2	1
287	428	NH NH2	0.7	0.7	1

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24) EC ₅₀ (μM)
288	429	OMe NH2	4	0.9	1
289	430	OMe NH2	5	0.7	1
290	431	F F F	5	5	
291	432	MeO NH2 MeO OMe	2	1	3
292	432	MeO H N H N NH2	2	0.6	1
293	434	Me O OMe	4	0.6	2
294	435	NH2 NH2	3 .	0.6	1
295	436	D NH ₂	5	0.8	5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
296	437	H ₃ C ₃	3	0.4	1
297	438	H NH ₂	5	0.6	1
298	439	MeO OMe N H NH2	3	0.4	1
299	440	H ₃ C O H NH ₂	4	0.1	2
300	441	H ₃ C ₀ H ₃	2	0.8	2
301	442	MeO N N N N N N N N N N N N N N N N N N N	17	0.4	1
302	443	H ₃ C, CH ₃ H ₃ C, CH ₃ N N N N N N N N N N N N N N N N N N N			
303	444	OH ON NH2 MeO OMe			

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (µM)	H4 Ac (T24 EC ₅₀ (μM)
304	445	MeO H NH ₂	16	6	
305	446	H N N N N N N N N N N N N N N N N N N N	21	7	
307	448	H ₃ C N NH NH ₂	3	0.2	2
308	449	O NH NH ₂	1	6	
309	450	H NH2	3	2	
310	451	S N H NH NH2	4	0.2	3
311	452	S-ON NH NH2	3	0.3	2
312	453	CH ₃ H NH ₂	9999	37	
313	454	CH ₃ H NH NH ₂	4	2	5

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (µM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
314	455	O NH NH ₂	4	0.7	1
315	456	HNMe—S	3	0.4	8888
316	457	MeO H ₂ N NH ₂	9999	9999	
317	458	H ₃ C NH ₂	3	0.3	2
318	459	NH NH ₂	4	0.3	. 1
319	460	H NH NH2	3	1	1
320	461	H ₃ C ₁ N ₁ H ₂ NH ₂ NH ₂ NH ₂ NH ₂ NH ₃ C ₁ C ₁ H ₃ NH ₂ NH ₂ NH ₂ NH ₃ NH ₂ NH ₃ NH ₂ NH ₃	1.4	0.3	1
321	462	N H NH ₂ N ₃ C	4	0.3	1
322	463	OH NH ₂	12	6	

Ex	Cpd	Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
323	464	H ₃ C N N NH ₂	4	11	
324	465	NH2	2	9999	9999
325	466	NH ₂	3	2	1
326	467	H NH ₂	4	0.4	2
327	468	H NH2	2	8	<1
426	571	MeO H OH OH	4	11	
427	572	MeO OMe	1.5	5	5
428	573	ON OUT HAN HAN HAN S	7	0.4	1
429	574	MeO NH ₂	13	0.7	3

Ex	Cpd	· Structure	Human HDAC-1 IC ₅₀ (μM)	MTT (HCT116) IC ₅₀ (μM)	H4 Ac (T24) EC ₅₀ (μM)
430	575	H ₃ C N S N S	2	0.2	1
431	576	H ₃ C ₀ NH NH ₂	5	. 6	
432	577	H ₃ C N O H NH ₂	2	0.5	2
433	578	MeO N H NH ₂	0.6	0.1	1
434	579	H ₃ C - S - NH ₂	2	0.5	1
435	580	MeN N N N N N N N N N N N N N N N N N N	4	0.3	<1
436	587	MeO OMe	5	0.8	2
437	590	MeO HN-HN-N	2	2	.3
438	591	MeO-NH H ₂ N	4	0.3	<1
439	592	MeO HN H2N	5	0.4	<1

Assay Example 2

Antineoplastic Effects of Histone Deacetylase Inhibitor son Human Tumor Xenografts In Vivo

Eight to ten week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) [0397] were injected subcutaneously in the flank area with 2 x 10⁶ preconditioned HCT116 human colorectal carcinoma cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under Forene anesthesia (Abbott Labs, Geneve, Switzerland). When the tumors reached a mean volume of 100 mm³, the mice were treated intravenously, subcutaneously, or intraperitoneally by daily injection, with a solution of the histone deacetylase inhibitor in an appropriate vehicle, such as PBS, DMSO/water, or Tween 80/water, at a starting dose of 10 mg/kg. The optimal dose of the HDAC inhibitor was established by dose response experiments according to standard protocols. Tumor volume was calculated every second day post infusion according to standard methods (e.g., Meyer et al., Int. J. Cancer 43: 851-856 (1989)). Treatment with the HDAC inhibitors according to the invention caused a significant reduction in tumor weight and volume relative to controls treated with vehicle only (i.e., no HDAC inhibitor). In addition, the level of histone acetylation when measured was significantly elevated relative to controls. Data for selected compounds are presented in Table 6. FIG. 1 shows the full experimental results for compound 106, which inhibits tumor growth by 80%. Figs. 2-10 show the results of additional compounds tested.

Table 6
Antitumor Activity in HCT 116 Colorectal Tumor Model In Vivo

Compound	% Inhibition of Tumor Growth
106	80ª
126	62 ^b
9	51 ^b
87	30 ^b
157	66ª
167	58ª
15	26 ^b
168	26 ^b
16	50 ^b
154	23ª
98	52³

a: 20 mg/kg i.p.

b: 40 mg/kg i.p.

Table 7

Antineoplastic Effects Of Histone Deacetylase Inhibitors On Nude Mice Xenograft Models

	% Inhibition Of Tumor Growth				
cpd	A 549 (p.o.)	SW48 (p.o.)	A 549 (i.p.)	HCT 116 (i.p.)	SW 48 (i.p.)
106	40% (70 mg/kg)	16% (60 mg/kg)			••
164	42% (70 mg/kg)	62% (60 mg/kg)	•	37% (20 mg/kg)	99% (25 mg/kg)
228	45% (70 mg/kg)	25% (60 mg/kg)	64% (20 mg/kg)	45% (20 mg/kg)	68% (20 mg/kg)
424b	67% (50 mg/kg)	78% (30 mg/kg)	60% (50 mg/kg)	77% (75 mg/kg)	68% (25 mg/kg)

Assay Example 3

Combined Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells *In Vivo*

[0398] The purpose of this example is to illustrate the ability of the combined use of a histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to enhance inhibition of tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

[0399] As described in Example 126, mice bearing implanted HCT116 tumors (mean volume 100 mm³) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

[0400] Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice are similarly established which receive no treatment (e.g., saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

[0401] Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitor according to the invention causes a significant reduction in tumor weight and volume relative to controls.

We claim:

1. A histone deacetylase inhibitor of formula (1):

$$R^{3}$$
 N
 N
 N
 N
 Y^{1}
 N
 Y^{2}
 Y^{2}
 Y^{2}
 Y^{3}
 Y^{2}
 Y^{3}
 Y^{4}
 Y^{2}
 Y^{3}
 Y^{4}
 Y^{2}
 Y^{3}
 Y^{4}
 Y^{4}

or a pharmaceutically acceptable salt thereof, wherein

 R^3 and R^4 are independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and L^1 - Cy^1 , wherein

L1 is C1-C6 alkyl, C2-C6 heteroalkyl, or C3-C6 alkenyl; and

Cy¹ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; or

R³ and R⁴ are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring is optionally substituted, and optionally forms part of a bicyclic ring system, or is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems is optionally substituted;

 Y^1 is selected from the group consisting of -N(R^1)(R^2), -CH₂-C(O)-N(R^1)(R^2), halogen, and hydrogen, wherein

 R^1 and R^2 are independently selected from the group consisting of hydrogen, $L^1,\,Cy^1,\,$ and $\,L^1-Cy^1,\,$ wherein

 L^1 is $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ heteroalkyl, or $C_3\text{-}C_6$ alkenyl; and

Cy¹ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted; or

 ${\sf R}^1$ and ${\sf R}^2$ are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the

group consisting of C, O, S, and N, and wherein the ring is optionally substituted, and optionally forms part of a bicyclic ring system, or is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems is optionally substituted;

 Y^2 is a chemical bond or N(R⁰), where R⁰ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

 Ak^1 is C_1 - C_6 alkylene, C_1 - C_6 -heteroalkylene (preferably, in which one -CH₂- is replaced with -NH-, and more preferably -NH-CH₂-), C_2 - C_6 alkenylene or C_2 - C_6 alkynylene;

 Ar^1 is arylene or heteroarylene, either of which is optionally substituted; and Z^1 is selected from the group consisting of

wherein Ay1 is aryl or heteroaryl, each of which is optionally substituted.

- 2. The compound according to claim 1 wherein Ay¹ is phenyl or thienyl, each substituted with OH or -NH₂.
- 3. The compound according to claim 2 wherein the amino or hydroxy substituent is ortho to the nitrogen to which Ay² is attached.
- 4. The compound according to claim 1 wherein Ay¹ is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl.
- 5. The compound according to claim 1 wherein Z^1 is

- 6. The compound according to claim 1 wherein Ar¹ is phenylene.
- 7. The compound according to claim 1 wherein Ak¹ is alkylene.
- 8. The compound according to claim 1 wherein Ak¹ is methylene.

- 9. The compound according to claim 1 wherein Y² is -NH-.
- 10. The compound according to claim 1 wherein Y^1 is $-N(R^1)(R^2)$ or $-CH_2-C(O)-N(R^1)(R^2)$.
- 11. The compound according to claim 10 wherein R¹ and/or R² are hydrogen.
- 12. The compound according to claim 10 wherein R¹ and/or R² are C₁-C₆ alkyl or C₂-C₆ alkenyl.
- 13. The compound according to claim 10 wherein R¹ and/or R² are allyl.
- 14. The compound according to claim 10 wherein R¹ and/or R² are aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally are substituted and optionally fused to one or two aryl rings.
- 15. The compound according to claim 14 wherein R¹ and/or R² are independently are phenyl, pyridyl, or pyrrolyl.
- 16. The compound according to claim 10 wherein R¹ and/or R² are independently cycloalkyl which is optionally substituted and optionally fused to one or two aryl rings
- 17. The compound according to claim 16 wherein R¹ and/or R² are independently cyclopropyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted and optionally fused to one or two aryl rings.
- 18. The compound according to claim 16 wherein R¹ and/or R² are independently cyclopropyl, cyclopentyl, or cyclohexyl.
- 19. The compound according to claim 1 wherein R³ and/or R⁴ are hydrogen.
- 20. The compound according to claim 1 wherein R^3 and/or R^4 are independently C_1 - C_6 alkyl or C_2 - C_6 alkenyl.
- 21. The compound according to claim 20 wherein R³ and/or R⁴ are allyl.

22. The compound according to claim 1 wherein R³ and/or R⁴ are independently aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which is optionally substituted and optionally fused to one or two aryl rings.

- 23. The compound according to claim 22 wherein R³ and/or R⁴ are independently phenyl, pyridyl, or pyrrolyl.
- 24. The compound according to claim 1 wherein R³ and/or R⁴ are independently cycloalkyl.
- 25. The compound according to claim 24 wherein R³ and/or R⁴ are independently cyclopropyl, cyclopentyl, or cyclohexyl, which is optionally substituted and optionally fused to one or two aryl rings.
- 26. The compound according to claim 24 wherein R³ and/or R⁴ are independently cyclopropyl, cyclopentyl, or cyclohexyl.
- 27. The compound according to claim 1 wherein L¹ is C₁-C₆ alkyl, C₂-C₆ heteroalkyl, or C₃-C₆ alkenyl.
- 28. The compound according to claim 27 wherein L¹ is C₁-C₆ alkylene
- 29. The compound according to claim 27 wherein L¹ is methylene or ethylene.
- 30. The compound according to claim 27 wherein L¹ is allyl.
- 31. The compound according to claim 1 wherein Cy¹ is heterocyclyl that is optionally substituted and optionally fused to one or two aryl rings
- 32. The compound according to claim 31 wherein Cy¹ is piperidine, pyrrolidine, piperazine, or morpholine, each of which is optionally substituted and optionally fused to one or two aryl rings.
- 33. The compound according to claim 31 wherein Cy¹ is piperidine, pyrrolidine, piperazine, or morpholine
- 34. The compound according to claim 1 wherein Cy¹ is cycloalkyl.

35. The compound according to claim 34 wherein Cy¹ is cyclopropyl, cyclopentyl, or cyclohexyl.

- 36. The compound according to claim 1 wherein Cy¹ is aryl or heteroaryl each of which is optionally substituted and is optionally fused to one or two aryl rings.
- 37. The compound according to claim 36 wherein Cy¹ is phenyl, pyridyl, or pyrrolyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
- 38. The compound according to claim 36 wherein Cy1 is phenyl, pyridyl, or pyrrolyl.
- 39. The compound according to claim 36 wherein Cy¹ is fused to one or two benzene rings.
- 40. The compound according to claim 1 wherein Cy¹ has between one and about five substituents independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, and halo.
- 41. The compound according to claim 40 wherein the substituents independently selected from are methyl, methoxy, and fluoro.
- 42. The compound according to claim 1 wherein R¹ and R² together and/or R³ and R⁴ together, each with the adjacent nitrogen atom, form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring is optionally substituted and is optionally fused to one or two aryl rings.
- 43. The compound according to claim 42 wherein the 5- or 6-membered ring is pyrrolidine, piperidine, piperazine, or morpholine, and wherein each ring is optionally substituted and optionally fused to an aryl ring.
- 44. The compound according to claim 43 wherein the aryl ring is benzene.
- 45. The compound according to claim 43 wherein the substituent comprises an aryl or C₃-C₁₂ cycloalkyl ring, either of which is optionally substituted and optionally fused to a C₃-C₁₂ cycloalkyl, aryl, heteroaryl, or heterocyclic ring.

- 46. The compound according to claim 44, wherein the substituent is phenyl, phenylmethyl, or phenylethyl, the phenyl ring of each of which is optionally fused to a C₁-C₁₂ cycloalkyl, aryl, or heterocyclic ring.
- 47. A histone deacetylase inhibitor of formula 1(a):

(la)

or a pharmaceutically acceptable salt thereof, wherein

J is C_1 - C_3 -hydrocarbyl, -N(R^{20})-, -N(R^{20})-CH₂-, -O-, or -O-CH₂-;

R²⁰ is H or Me;

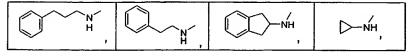
X and Y are independently selected from -NH₂, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A $(C_1-C_6$ -alkyl)_n-B-;

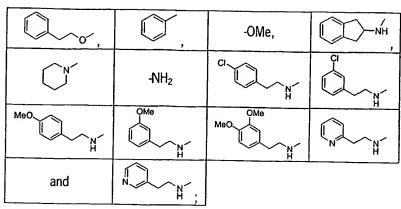
A is H, C_1 - C_6 -alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -0-, or a direct bond; and

n is 0 (in which case A is directly bonded to B) or 1.

- 48. The compound according to claim 47 wherein A is phenyl optionally substituted with one or more moieties selected from halo and methoxy, and B is -NH-.
- 49. The compound according to claim 47 wherein A is selected from cyclopropyl, pyridinyl, and indanyl.
- 50. The compound according to claim 47 wherein J is -NH-CH₂-, -O-CH₂-, -N(CH₃)-CH₂-, -CH=CH-, or -CH₂-CH₂-.
- 51. The compound according to claim 47 wherein R²⁰ is -H.
- 52. The compound according to claim 47 wherein X is selected from





and Y is selected from

-NH₂,	D-NH,	Δ _N ,	n-BuNH,
MeOCH₂CH₂NH,	HN,	OMe HN	G P
OMe OMe	OMB HN	HN,	Ŷ.
H	Ме	-OMe	CH ₃ (CH ₂) ₃ NH-
and	CH ₃ O(CH ₂) ₂ -NH		

53. The compound according to claim 47 wherein J, X, and Y are selected from the following combinations:

Cpd	J	Х	Υ
204	-NH-	NH NH	-NH ₂
207	-OCH₂-	NH NH	-NH ₂
210	-NHCH₂-	The state of the s	Н
212	-NHCH ₂ -	-OMe	-OMe
214	-NHCH₂-	NH NH	-OMe
216	— NСН ₂ - СН ₃	NH NH	-Me
218	-NHCH₂-	NH NH	-Me

Cpd	J	X	Υ
220	-CH=CH-	-NH ₂	-NH ₂ -
223	-CH=CH-	○ N	-NH₂
224	-CH ₂ CH ₂ -	-NH ₂	-NH ₂
470	-NHCH ₂ -	H N N	NH ₂
471	-NHCH₂-		D—и́н
472	-NHCH₂-	NH NH	△ H N
473	-NHCH₂-		n-BuNH

Cpd	J	X	Y
474	-NHCH₂-	THE YEAR OF THE PROPERTY OF TH	MeO(CH2)₂NH
475	-NHCH ₂ -	 	<u>+</u> -
476	-NHCH₂-	D—√H	OMe
477	-NHCH₂-	⊳–ńH	HZ-CI-
478	-NHCH₂-	D—vH	OMe OMe HN

Cpd	J	X	Υ
479	-NHCH ₂ -	∕√м́н	OMe
480	-NHCH ₂ -	<u></u>	HN
481	-NHCH₂-		-H-
482	-NHCH ₂ -		. ⊳_ńH
483	-NHCH ₂ -		Ме
484	-NHCH₂-		NH ₂
	•	and	
485	-NHCH ₂ -	NH NH	

(2)

54. A histone deacetylase inhibitor of formula (2):

$$Cy^2-X^1-Ar^2$$

$$R^5 O N Ay^2$$

$$R^6 Q N Ay^2$$

or a pharmaceutically acceptable salt thereof, wherein

Cy² is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

 $\rm X^1$ is selected from the group consisting of a covalent bond, $\rm M^1L^2\text{-}M^1$, and $\rm L^2\text{-}M^2L^2$ wherein

 L^2 , at each occurrence, is independently selected from the group consisting of a chemical bond, C_1 - C_4 alkylene, C_2 - C_4 alkenylene, and C_2 - C_4 alkynylene, provided that L^2 is not a chemical bond when X^1 is M^1 - L^2 - M^1 :

 M^1 , at each occurrence, is independently selected from the group consisting of -O-, -N(R^7)-, -S-, -S(O)-, S(O)₂-, -S(O)₂N(R^7)-, -N(R^7)-S(O)₂-, -C(O)-, -C(O)-NH-, -NH-C(O)-, -NH-C(O)-O-and -O-C(O)-NH-, wherein R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

M² is selected from the group consisting of M¹, heteroarylene, and heterocyclylene, either of which rings is optionally substituted;

Ar2 is arylene or heteroarylene, each of which is optionally substituted;

 $\mbox{\sc R}^{\mbox{\sc 5}}$ and $\mbox{\sc R}^{\mbox{\sc 6}}$ are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

q is 0 or 1; and

 Ay^2 is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which Ay^2 is attached) and further optionally substituted;

provided that when Cy^2 is naphthyl, X^1 is $-CH_2$ -, Ar^2 is phenyl, R^5 and R^6 are H, and q is 0 or 1, Ay^2 is not phenyl or o-hydroxyphenyl.

- The compound according to claim 54 wherein when Ay² is o-phenol optionally substituted by halo, nitro, or methyl, Ar² is optionally substituted phenyl, X¹ is -O-, -CH₂-, -S-, -S-CH₂-, -S(O)-, -S(O)₂-, -C(O)-, or -OCH₂-, then Cy² is not optionally substituted phenyl or naphthyl.
- The compound according to claim 54 wherein when Ay² is o-anilinyl optionally substituted by halo, C₁-C₆-alkyl, C₁-C₆-alkoxy or -NO₂, q is 0, Ar² is phenyl, and X¹ is -CH₂-, then Cy² is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).
- 57. The compound according to claim 54 wherein when X¹ is -CH₂-, Ar² is optionally substituted phenyl, q is 1, and R⁶ is H, then Cy² is not optionally substituted imidazole.

58. The compound according to claim 54 wherein when Ar² is amino or hydroxy substituted phenyl, X¹ is C₀-C₈-alkyl-X^{1a}- C₀-C₈-alkyl, wherein X^{1a} is -CH₂-, -O-, -S-, -NH-, -C(O)-, then Cy² is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.

- 59. The compound according to claim 54 wherein when Ay^2 is o-phenol, Ar^2 is substituted phenyl, X^1 is -O-, -S-, -CH₂-, -O-CH₂-, -S-CH₂-, or -C(0)-, and R^5 and R^6 are H, then Cy^2 is not optionally substituted naphthyl.
- 60. The compound according to claim 54 wherein when Ay² is o-anilinyl, q is 0, Ar² is unsubstituted phenyl, X¹ is -CH₂-, then Cy² is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.
- 61. The compound according to claim 54 wherein Ay² is phenyl or thienyl, each substituted with -OH or -NH₂.
- 62. The compound according to claim 54 wherein the amino or hydroxy substituent is ortho to the nitrogen to which Ay² is attached.
- 63. The compound according to claim 54 wherein Ay² is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl.
- 64. The compound according to claim 54 wherein

a is 1:

 M^1 , at each occurrence, is selected from the group consisting of -N(R^7)-, -S-, -C(0)-NH-, and -O-C(0)-NH-, where R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and

Ay² is anilinyl, which is optionally substituted.

- 65. The compound according to claim 64 wherein the -NH₂ group of Ay² is in an ortho position with respect to the nitrogen atom to which Ay² is attached.
- 66. The compound according to claim 65 wherein R⁵ and R⁶ are independently selected from the group consisting of hydrogen and C₁-C₄ alkyl.
- 67. The compound according to claim 65 wherein R⁵ and R⁶ are hydrogen.

68. The compound according to claim 54 wherein Ar² has the formula

and wherein G, at each occurrence, is independently N or C, and C is optionally substituted.

69. The compound according to claim 68 wherein Ar² has the formula

- 70. The compound according to claim 54 wherein Ar² is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolylene.
- 71. The compound according to claim 54 wherein X¹ is a chemical bond.
- 72. The compound according to claim 54 wherein X^1 is $L^2-M^2-L^2$, and M^2 is selected from the group consisting of -NH-, -N(CH₃)-, -S-, -C(O)-N(H)-, and -O-C(O)-N(H)-.
- 73. The compound according to claim 54 wherein X¹ is L²-M²-L², where at least one occurrence of L² is a chemical bond.
- 74. The compound according to claim 54 wherein X¹ is L²-M²-L², where at least one occurrence of L² is alkylene, preferably methylene.
- 75. The compound according to claim 54 wherein X¹ is L²-M²-L², where at least one occurrence of L² is alkenylene.
- 76. The compound according to claim 54 wherein X¹ is M¹-L²-M¹ and M¹ is selected from the group consisting of -NH-, -N(CH₃)-, -S-, and -C(O)-N(H)-.
- 77. The compound according to claim 54 wherein Cy² is aryl or heteroaryl, each optionally substituted.
- 78. The compound according to claim 54 wherein Cy² is phenyl, pyridyl, imidazolyl, or quinolyl, each of which is optionally substituted.

- 79. The compound according to claim 54 wherein Cy² is heterocyclyl.
- 80. The compound according to claim 54 wherein Cy2 is

each of which is optionally substituted and is optionally fused to one or two aryl rings.

- 81. The compound according to claim 54 wherein Cy² has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy.
- 82. The compound according to claim 54 wherein the substituents are selected from methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl
- 83. The compound of claim 54 of structural formula (2a):

$$\begin{array}{c|c}
O \\
NH \\
R^6 & Ar^a \\
NH_2
\end{array}$$
(2a)

wherein

Ara is phenyl or thienyl;

R⁶ is H, or C₁-C₆-alkyl (preferably -CH₃);

Y and Z are independently -CH= or -N=;

W is halo, (V'-L4),-V-L3-;

 L^3 is a direct bond, $-C_1-C_6$ -hydrocarbyl, $-(C_1-C_3-hydrocarbyl)_{m1}-X'+(C_1-C_3-hydrocarbyl)_{m2}$, $-NH+(C_0-C_3-hydrocarbyl)$, $-(C_1-C_3-hydrocarbyl)-NH-$, or $-NH+(C_1-C_3-hydrocarbyl)-NH-$;

m1 and m2 are independently 0 or 1;

X' is $-N(R^{21})$ -, $-C(O)N(R^{21})$ -, $N(R^{21})C(O)$ -, -O-, or -S-;

R²¹ is -H, V"-(C₁-C₆-hydrocarbyl)_c;

L4 is (C₁-C₆-hydrocarbyl)_a-M-(C₁-C₆-hydrocarbyl)_b;

a and b are independently 0 or 1;

M is -NH-, -NHC(O)-, -C(O)NH-, -C(O)-, -SO₂-, -NHSO₂-, or -SO₂NH-

V, V', and V'' are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the $\mathcal A$ and Ar^a rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

84. The compound according to claim 83 wherein:

Y and Z are -CH= and R^6 is H;

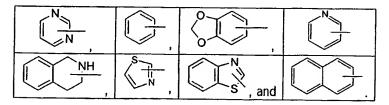
W is V-L³;

L3 is -NH-CH- or --CH-NH-:

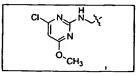
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, C₁-C₆-hydrocarbyl, C₁-C₆-hydrocarbyl-oxy or -thio (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

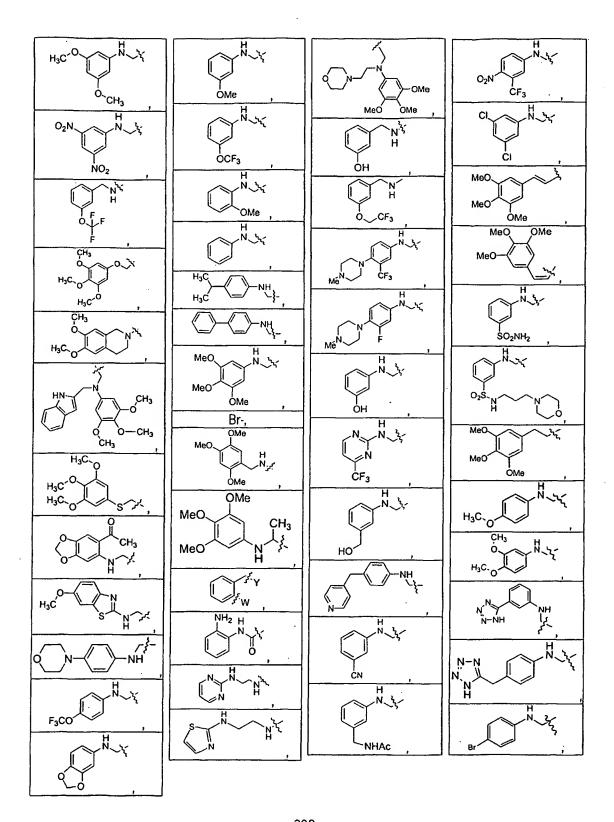
Ara is phenyl and the amino moieties to which it is bound are ortho to each other.

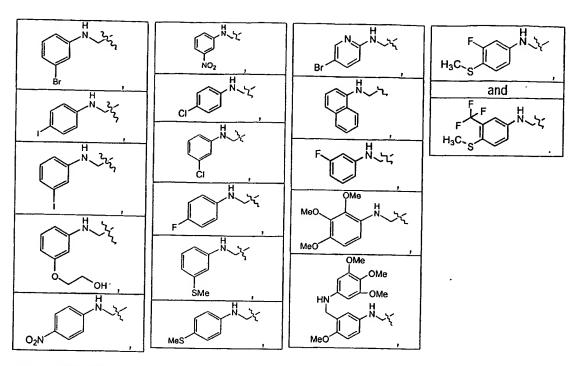
85. The compound according to claim 83 wherein V is an optionally substituted ring moiety selected from:



86. The compound according to claim 83 wherein W is selected from:,







- 87. The compound according to claim 83 wherein the \mathcal{A} and Ara rings are not further substituted.
- 88. The compound according to claim 83 selected from the following, in which, unless expressly displayed otherwise, Ar^a is phenyl:

Cpd	W	Y	Z	R ⁶
481	H ₃ C O H ₃ C O H ₃ C, O H ₃ C	СН	СН	Н
484	H ₃ C,O H ₃ C,O H ₃ C,O		ih Nh	†2
492	H ₃ C ^{-O} N H N Y	СН	СН	Н
493	CI N N Y	СН	СН	Н

Cpd	W	Y	Z	R ⁶
494	H ₃ C ² O _{CH₃}	СН	СН	Н
495	O ₂ N , , , , , , , , , , , , , , , , , , ,	СН	СН	Н
496	P F F	СН	СН	Н
497	CH ₃ O > Y H ₃ C O	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
498	CH ₃ N ² i	СН	СН	Н
499	HN CH ₃	СН	сн	Н
500	H ₃ C.0 H ₃ C.0 S.2.4	СН	СН	Н
501	O NET	СН	СН	Н
502	O CH ₃	СН	СН	н
503	0_N-{\rightarrow}-NH	СН	СН	Н
504	F ₃ CO H N \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	СН	СН	Н
505	J. Y.	СН	СН	н
506	OCF ₃	СН	СН	Н
507	H N X	СН	СН	Н
508	H N OMe H	СН	СН	Н
509	O N X	СН	СН	Н
510	H ₂ C H ₃	СН	СН	Н

Cpd	W	Υ	Z	R ⁶
511	N.Y.	СН	ĊН	Н
512	MeO H	СН	N	Н
516	Br-	СН	СН	CH₃
517	OMe MeO H N ₃ ,r	СН		CH₃
518	OMe MeO CH ₃	СН	СН	СН₃
519	Of W	СН	СН	Н
520	NH ₂ H	СН	СН	Н
521	Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	N	СН	Н
522	S N H	N	СН	Н
523	MeO N N N N N N N N N N N N N N N N N N N	СН	СН	Н
524	OH N,	N	СН	н
525	N H O_CF ₃	N	CH	Н
526	Me ^N CF ₃	СН	СН	Н

Cpc		Y	Z	R ⁶
527	Mé ^N F	Cł	1 CF	Н
528	AN N	Cŀ	1 СН	Н
529	N H Y N CF3	CH	СН	Н
530	HO	СН	СН	Н
531		СН	СН	Н
532	H N. J.	СН	СН	Н
533	NC H, 'z ₁ '	СН	СН	Н
534	O ₂ N CF ₃	СН	CH	Н
535	CI	СН	СН	Н
536	MeO MeO	СН	СН	Н
537	MeO OMe	СН	СН	Н

Сро	W	Y	Z	R ⁶
538	H N V	CH		
539	N.X	CH	I CF	І Н
540	MeO YY	СН	СН	Н
541	H ₃ C ₀	СН	СН	Н
542	H ₃ C H	СН	СН	Н
543	7-2-12 HZ Z-12 Z-12 Z-12 Z-12 Z-12 Z-12 Z-12 Z-1	СН	СН	н
544	N. H. N. Y.	СН	СН	Н
545	Br N Y	СН	СН	Н
546	H N N Vi N	СН	СН	Н
547	, N. Y.	СН	СН	н
548	H Z Z Z Z	СН	СН	Н
549	OH NO H	СН	СН	Н

				-6
Cpd	W	Υ	Z	R ⁶
550	O _Z N H	СН	СН	Н
551	H, J,	СН	СН	Н
552	CI HI 'Y'	СН	СН	Н
553		СН	СН	Н
554	F LX	СН	СН	Н
555	H YY	СН	СН	Н
556	Mes N Z	СН	СН	Н
557	N H 77	СН	СН	Н
558		СН	СН	Н
559	F \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	СН	СН	Н
560	MeO H OMe OMe	NH C	NH2	
561	MeO J H	O H	OH	

Cpd	W	Υ	Z	R ⁶
562	MeO HN 1	СН	ĊН	Н
563	OMe OMe OMe NH	СН	сн	Ξ
564	MeO H H H H H H H H H H H H H H H H H H H		,NH ₂	•
565	H ₃ C ₂ S	СН	СН	н
566	FF F N. X	СН	СН	Н
567	MeO OMe		I NH	
568	MeO H ₂ N H N N N N N N N N N N N N N N N N N N		1	H ₂ H ₂
569	H ₃ C-0 13	СН	N	Н
570	CH ₃ O NH H ₃ C-O	,—	H ₂ N N — ⟨	s

89. The compound according to claim 88 wherein the amide nitrogen and the amino nitrogen bound to Ar^a are *ortho* to each other)

90. The compound according to claim 54, the invention comprises compounds of the formula (2b):

$$Cy^2 \xrightarrow{X^1} Q \xrightarrow{Q} N \xrightarrow{A} Ay^2$$
(2b)

or a pharmaceutically acceptable salt thereof, wherein

Ay 2 is phenyl or thienyl, each substituted at the ortho position with -NH $_2$ or -OH and each further optionally substituted with one to three substituents independently selected from -NH $_2$, -OH, and halo;

q is 0 or 1:

 X^1 is selected from -CH₂-, -NH-CH₂-, and -S-CH₂-;

 Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3 -, CH_3O -, phenyl optionally substituted with one to three CH_3O -, morphylinyl, morphylinyl- C_1 - C_3 -alkoxy, cyano, and $\text{CH}_3\text{C}(\text{O})\text{NH}$ -;

provided that when Cy² is naphthyl, X¹ is -CH₂-, and q is 0 or 1, Ay² is not o-hydroxyphenyl.

91. The compound according to claim 90 wherein Ay2 is selected from:

$$\overset{\text{NH}_2}{\longleftarrow}, \qquad \overset{\text{NH}_2}{\longleftarrow} \text{ and } \qquad \overset{\text{NH}_2}{\longleftarrow};$$

- 92. The compound according to claim 90 wherein Cy² is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinozolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three CH₃O-.
- 93. The compound according to claim 90 wherein Cy² is phenyl substituted with one to three CH₃O-.

94. A histone deacetylase inhibitor of formula (3):

(3)

or a pharmaceutically acceptable salt thereof, wherein

Ar³ is arylene or heteroarylene, either of which is optionally substituted;

Cy³ is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

provided that when Cy^3 is a cyclic moiety having -C(O)-, -C(S)-, -S(O)-, or -S(O)₂- in the ring, then Cy^3 is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

 X^2 is selected from the group consisting of a chemical bond, L^3 , W^1-L^3 , L^3-W^1 , $W^1-L^3-W^1$, and $L^3-W^1-L^3$, wherein

 W^1 , at each occurrence, is S, O, or $N(R^9)$, where R^9 is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

 L^3 is $C_1\text{-}C_4$ alkylene, $C_2\text{-}C_4$ alkenylene, or $C_2\text{-}C_4$ alkynylene;

provided that X^2 does not comprise a -C(O)-, -C(S)-, -S(O)-, or -S(O)₂- group; and further provided that when Cy^3 is pyridine, then X^2 is L^3 , W^1 - L^3 , or L^3 - W^1 .

95. The compound according to claim 94 wherein Ar³ has the structure:

wherein Q, at each occurrence, is independently N or C, and C is optionally substituted;

- 96. The compound according to claim 94 wherein X² is selected from the group consisting of L³, W¹-L³, L³-W¹, W¹-L³-W¹, and L³-W¹-L³.
- 97. The compound according to claim 94 wherein when X² is a chemical bond, then Ar³ is not

- and Cy3 is not the radical of a substituted or unsubstituted diazepine or benzofuran.
- 98. The compound according to claim 95 wherein Q at each occurrence is C(R⁸), where R⁸ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy.
- 99. The compound according to claim 95 wherein from one to about three Q are nitrogen.
- 100. The compound according to claim 94 wherein Ar³ is selected from the group consisting of phenylene, pyridylene, thiazolylene, and quinolylene.
- 101. The compound according to claim 94 wherein X² is a chemical bond.
- 102. The compound according to claim 94 wherein X² is a non-cyclic hydrocarbyl.
- 103. The compound according to claim 94 wherein X² is alkylene.
- 104. The compound according to claim 94 wherein X² methylene or ethylene.
- 105. The compound according to claim 94 wherein X² alkenylene or alkynylene.
- 106. The compound according to claim 102 wherein one carbon in the hydrocarbyl chain is replaced with -NH- or -S-.
- 107. The compound according to claim 94 wherein X² is W¹L³-W¹ and W¹ is -NH- or -N(CH₃)-.
- 108. The compound according to claim 94 wherein Cy³ is cycloalkyl.
- 109. The compound according to claim 94 wherein Cy³ is cyclohexyl.
- 110. The compound according to claim 94 wherein Cy³ is aryl or heteroaryl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
- 111. The compound according to claim 94 wherein Cy³ is phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.

112. The compound according to claim 94 wherein the cyclic moiety of Cy³ is fused to a benzene ring.

- 113. The compound according to claim 94 wherein Cy³ has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl.
- 114. The compound according to claim 113 wherein the substituents are selected from methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl.
- 115. The compound according to claim 94 wherein Cy³ has from one to three substituents of the formula –K¹-N(H)(R¹0), wherein

K1 is a chemical bond or C1-C4 alkylene;

R¹⁰ is selected from the group consisting of Z' and -Ak²-Z', wherein

Ak² is C₁-C₄ alkylene; and

Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted, and each of which is optionally fused to one or two aryl or heteroaryl rings, or to one or two saturated or partially unsaturated cycloalkyl or heterocyclic rings.

116. The compound according to claim 115 wherein the substituent is selected from

- 117. The compound according to claim 94 wherein Cy³ is heterocyclyl, each of which is optionally substituted and is optionally fused to one or two aryl rings.
- 118. The compound according to claim 94 wherein Cy³ is selected from

119. The compound according to claim 117 wherein the heterocycle of Cy³ is fused to a benzene ring.

- 120. The compound of claim 94 wherein when Ar⁴ is quinoxalinylene, then X³ is not -CH(OH)-.
- 121. The compound of claim 94 wherein Ar³ is

and X is -CH₂-, -NH-, O, or S.

122. The compound of claim 94 wherein Ar³ is

and X is S or O.

The compound according to claim 54 wherein Ay² is ortho-anilinyl;
 q is 0; and
 X¹ is M¹-L²-M¹ or L²-M²-L².

- 124. The compound according to claim 123 wherein Ar² is aryl or heteroaryl; and Cy²-X¹- is collectively selected from the group consisting of
 - a) $A_1 \cdot L_1 \cdot B_1$ -, wherein A_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_1 is $-(CH_2)_{0\cdot 1}NH(CH_2)_{0\cdot 1}$ -, -NHC(O)-, or $-NHCH_2$ -; and wherein B_1 is phenyl or a covalent bond;
 - b) A_2 - L_2 - B_2 -, wherein A_2 is CH_3 ($C=CH_2$)-, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L_2 is -C=C-; and wherein B_2 is a covalent bond;

c) A₃-L₃-B₃-, wherein A₃ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₃ is a covalent bond; and wherein B₃ is – CH₂NH-;

- d) $A_4-L_4-B_4$, wherein A_4 is an optionally substituted aryl; wherein L_4 is -NHCH₂-; and wherein B_4 is a thienyl group;
- e) A_5 - L_5 - B_5 -, wherein A_5 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_5 is a covalent bond; and wherein B_5 is -SCH₂-;
- f) morpholinyl-CH₂-
- g) optionally substituted aryl;
- h) A_6 - L_6 - B_6 -, wherein A_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_6 is a covalent bond; and wherein B_6 is NHCH₂-;
- i) $A_7L_7B_7$, wherein A_7 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_7 is a covalent bond; and wherein B_7 is $-CH_2$ -;
- j) aptionally substituted heteroaryl or optionally substituted heterocyclyl;
- k) A_8L_8 - B_8 -, wherein A_8 is optionally substituted phenyl; wherein L_8 is a covalent bond; and wherein B_8 is -O-;
- A₉-L₉-B₉-, wherein A₉ is an optionally substituted aryl; wherein L₉ is a covalent bond; and wherein B₉ is a furan group;
- m) $A_{10}-L_{10}-B_{10}$, wherein A_{10} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{10} is $-CH(CH_2CH_3)$ -; and wherein B_{10} is $-NHCH_2$ -;
- n) A₁₁-L₁₁-B₁₁-, wherein A₁₁ is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₁ is a covalent bond; and wherein B₁₁ is –OCH₂-;
- A₁₂-L₁₂-B₁₂-, wherein A₁₂ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₂ is-NHC(O)-; and wherein B₁₂ is N(optionally substituted aryl)CH₂-;
- p) $A_{13}L_{13}B_{13}$, wherein A_{12} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{13} is a covalent bond; and wherein B_{13} is NHC(0)-;

q) $A_{14}L_{14}$ - B_{14} -, wherein A_{14} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{14} is-NHC(O)(optionally substituted heteroaryl); and wherein B_{14} is -S-S-;

- r) F₃CC(0)NH-;
- s) A_{15} - B_{15} -, wherein A_{15} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{15} is- $(CH_2)_{0-1}NH$ (optionally substituted heteroaryl)-; and wherein B_{15} is - $NHCH_2$ -;
- t) $A_{16}L_{16}$ - B_{16} -, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is N(optionally substituted alkyl)CH₂-; and
- u) A₁₆-L₁₆-B₁₆-, wherein A₁₆ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁₆ is a covalent bond; and wherein B₁₆ is (optionally substituted aryl-CH₂)₂-N-.
- 125. The compound according to claim 123 wherein Cy²-X¹- is collectively selected from the group consisting of
 - a) D₁-E₁-F₁-, wherein D₁ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E₁ is -CH₂- or a covalent bond; and wherein B₁ is a covalent bond:
 - b) D_2 - E_2 - F_2 -, wherein D_2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_2 is -NH(CH₂)₀₋₂-; and wherein F_2 is a covalent bond;
 - c) D_3 E₃F₃-, wherein D_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E₃ is -(CH₂)₀₋₂NH-; and wherein F₃ is a covalent bond;
 - d) D_4 - E_4 - F_4 -, wherein D_4 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_4 is $-S(CH_2)_{0\cdot 2^-}$; and wherein F_4 is a covalent bond;
 - e) D₅-E₅-F₅-, wherein D₅ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E₅ is -(CH₂)₀₋₂S-; and wherein F₅ is a covalent bond; and

f) D_6 - E_6 - F_6 , wherein D_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_6 is -NH(CH₂)₀₋₂NH-; and wherein F_6 is a covalent bond.

126. The compound of claim 54 having formula (3b):

wherein Y and Z are independently N or CH and W is selected from the group consisting of:

	H₃C OH	<u></u> }-
CI NH	NH2 H	MeO H H H
MeO H	H ₂ C CH ₃	ОН
CI NH	S NH	MeO OMe
N H S S	N H S S S	N S N H
O N vi	MeO NeO OMe	NH2 NH2 NH2
HN N N N N N N N N N N N N N N N N N N	HN N N	N HN X
O N St.	H NH	CI N Me

N gr	MeO N N	F N J
O N N CH ₃		Br N Me
S N S P C	N O O O O O O O O O O O O O O O O O O O	Br N Jrt
Br N rr	Br N N	CI N N
F N N 3º	F F N N SFL	S N S F
Ph N	Me N N	N N N N N N N N N N N N N N N N N N N
ON NON	H3C O.N	N N N N N N N N N N N N N N N N N N N
N N N	HN S	Ph—NC Me
H CN N S Me		O CN
	OH OH	O'str.

MeO 235	MeO N N	CI N CH ₃
Br NH O NO N	MeO ONE OME	CI—NH OME
ONH OME	O—NH OME	NH ₂ H
N N ZZ	H ₃ C N S X	F N S ZZ
NH ₂ H	(N) S'SK	H ₃ C N H
H ₃ C N N N	H ₃ C N O Y	H ₃ C. O
OT NH	H ³ C O N N N	H ₃ C O H ₃ C O
N NH NH	H3C~ONNNY	S L'AG
H ₃ C, O, H, N,	H ₃ C O CH ₃	O _{CH3}
H ₃ C-O \ O \ \\ O \ \\ CH ₃		H ₃ C ⁻ O H Y
O NH NH ₂	N HN T	O H N J

		T
H3C N N N	N N ZZ	H ₃ C _O H _N >\(\frac{1}{2}\)
H ₃ C ₋₀ H ₋₂	H ₃ C ₀ H ₃ Z _i	H ₃ C O H Z ₁ C OH
H ₃ C H N \\ CH ₃	N N Y	H ₃ C
H ₃ C C H	ON N N N N	MeO N-1
F H	MeO H	F N 1
N-X-	H N F	CI N N Y
CI H N Y	H N N N N N N N N N N N N N N N N N N N	MeO N N
F ₃ CO H	H N OCF ₃	MeO Me
OCF ₃	F ₃ CO N- ¹ / _H	MeO H
	H N OMe	H N N N
F ₃ C N ³ -, H	MeO OMe	MeO H N N N N N N N N N N N N N N N N N N

·		
MeO N-1-	T N N N N N N N N N N N N N N N N N N N	HN N N
H N 12	H N SMe	MeO H N N N N N N N N N N N N N N N N N N
MeO H N N	H ₃ C _C O H N N OMe	MeO OMe H H N N N N N N N N N N N N N N N N N
H ₃ C CH ₃ H ₃ C CH ₃ O H ₃ C CH ₃ N V OMe	OH N - 12,- MeO OMe	N N N N N N N N N N N N N N N N N N N
F ₃ CO OCF ₃	MeO HN	o NH NH
O NH NH	MeO H NH ₂	O NH
MeO H ₂ N H ₂ N H ₂ N	MeO NH '\'\'	ON NH Y(
NH N	OH OH	H₃C S'Ä
HN	H N N N N N N N N N N N N N N N N N N N	HN-N H
MeO H N	ОН	OMe

127. The compound according to claim 126 wherein Y, Z and W are one of the following combinations:

Cpd	W	Υ	Z
164	MeO MeO OMe	СН	СН
165	но	N	СН
166	MeO-	СН	СН
167	MeO N	СН	Ν
168	MeO	СН	N
169	MeO N N N N N N N N N N N N N N N N N N N	СН	СН

Cpd	W	Υ	Z
170		СН	СН
171	MeO s	N	СН
172	S	СН	СН
174	F H	СН	N
175	F N	СН	N
176	MeO NH	СН	N
177	Ph N-N S	СН	СН
178	Z, Z,	N	СН

Cpd	W	Y	Z
179	N N	СН	СН
180	Me No	СН	СН
181		СН	СН
182	H ₃ C N S CH ₃	СН	СН
	and		
183	F F N S	СН	СН

128. The compound according to claim 126 wherein Y, Z and W are one of the following combinations:

Cpd	W	Υ	Z
187	N H	СН	СН
188	NH ₂ H	СН	СН
189	MeO H N N N N N N N N N N N N N N N N N N	СН	СН
190	MeO H	СН	СН
193	H ₂ C CH ₃	СН	СН
194	OH T	СН	СН
195	H ₃ C OH	СН	СН
196	<u></u> —=}-	СН	СН
320	CI NH	СН	СН
321	CI NH	СН	СН
322	Br NH	СН	СН
323	MeO OMe MeO HN	СН	СН

		<u>, , , , , , , , , , , , , , , , , , , </u>	
Cpd	. W	Υ	Z
325	N H S S	СН	СН
326	N N N S S S S S S S S S S S S S S S S S	СН	СН
327	Z N N N N N N N N N N N N N N N N N N N	СН	СН
328	ON SK	СН	СН
329	MeO OMe	СН	сн
330	H ₃ C N N N N N N N N N N N N N N N N N N N	СН	СН
331	HN NH2	СН	СН
332	HN CI	СН	СН
333	H ₃ C N N N N N N N N N N N N N N N N N N N	СН	СН
334	H NH	СН	СН
335	N Y	СН	СН

Cpd	W	Υ	Z
336	CI N J.f.	СН	СН
337	N Me	СН	СН
338	MeO N	СН	СН
339	F N Jrt	СН	СН
340	ON CH3	СН	СН
341		сн	СН
342	Br N Me	СН	СН
343	S N N N N N N N N N N N N N N N N N N N	СН	СН
344	Br N N	СН	СН
345	OMe	СН	СН
346	Br N Jrt	СН	СН

Cpd	W	Y	Z
347	Br N rt	СH	СН
348	CI N N N	СН	СН
349	F N N Y	СН	СН
350	F F N N SF.	СН	СН
351	S N Y	СН	СН
352	N ZZ	СН	СН
353	N N N	СН	СН
354	N N N	СН	СН
355	ON N-7's	ĊН	СН
356	H ₃ C O, N	СН	СН
357	N=O-N	СН	СН
358	N N N N N N N N N N N N N N N N N N N	СН	СН
359	HN-S	СН	СН

Cpd	W	Υ	Z
360	Ph————————————————————————————————————	СН	СН
361	TN Me	СН	СН
362		СН	СН
363	S O	СН	СН
364		СН	СН
365	он он	СН	СН
366	Ožri,	СН	СН
367	MeO Contraction	СН	СН
368	MeO N N	СН	СН
369	CI N HN CH ₃	СН	СН
370	Br NH NH O >	СН	СН

Cpd	W	Υ	Z
371	MeO O NH OMe	СН	СН
372	CI—NH OME	СН	СН
373	O N NH OMe	СН	СН
374	O—NH OMe	СН	СН
375	NH ₂ H	СН	СН
377	N 335	СН	СН
378	H₃C N S S S CH₂	СН	СН
379	F F N S	СН	СН
380	NH ₂ H	N	СН
381	N S S	СН	СН
382	H ₃ C N N N	СН	СН

Cpd	W	Υ	Z
383	H ₃ C N N N	СН	СН
384	CH ₃ N N	СН	СН
385	H ₃ C O	СН	СН
386	OT NOTE	СН	СН
387	H,C O N N N N N N N N N N N N N N N N N N	СН	СН
388	H ₃ C O H	СН	СН
389	N NH NH	СН	СН
390	H ₂ C O N H	СН	СН
391		СН	СН
392	H ³ C,O CH ³	СН	СН
393	H ₃ C O N N N N N N N N N N N N N N N N N N	СН	СН
394	сн _э s	СН	СН

Cpd	W	Y	Z
395	H ₃ C O O Y	СН	СН
396	O.J.	СН	СН
397	H ₃ C ⁻ O H X	СН	СН
398	O NH S S:}-	СН	N
399	= Z = Z = -	СН	СН
400	O N 37	СН	СН
401	H3C N N N	СН	СН
402	0 N−⟨ N+	СН	СН
403	H ₃ C, CH ₃	сн	СН
404	H ₃ C	СН	СН
405	H ₃ C ₀ H ₃ Z	СН	СН
406	H ₃ C-O H OH	СН	СН

Cpd	W	Υ	Z
407	H ₃ C H ₃	СН	СН
408	N=O-NH}	СН	СН
409	H ₃ C CH ₃ H	СН	СН
410	H ₃ C CH ₃	СН	СН
411		СН	СН
412	MeO N 1	СН	СН
413	F H	СН	СН
414	MeO H	СН	СН
415	F N Y	СН	СН
416	N-X H	СН	СН
417	H N X	СН	СН
418	CI N N N N N N N N N N N N N N N N N N N	СН	сн

Cpd	W	Υ	Z
419		СН	СН
420	HZ Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z Z	СН	СН
421	MeO N H	СН	СН
422	F ₃ CO HN - 1,-	СН	СН
423	OCF ₃	СН	СН
424b	MeO OMe	СН	СН
425	OCF ₃	СН	СН
426	F ₃ CO H	СН	СН
427	MeO H	СН	СН
428		СН	СН
429	H N OMe	СН	СН
430	H N N	СН	СН

Cpd	W	Υ	Z
431	O F₃C N ^{¹ζ} , H	СН	СН
432	MeO OMe	СН	СН
433	MeO H H N 34	СН	СН
434	MeO N N N N N N N N N N N N N N N N N N N	СН	СН
435	ON N N N	СН	СН
436	HN N N	СН	СН
437	MeS H	СН	СН
438	H N SMe	СН	СН
439	MeO H N N N N N N N N N N N N N N N N N N	СН	СН
440	MeO H H N N	СН	СН
441	H ₃ C O H N 12	СН	СН

Cpd	W	Y	Z
442	MeO OMe	СН	СН
443	H ₃ C CH ₃ H ₃ C CH ₃ OMe	СН	СН
444	MeO OMe	СН	СН
445	MeO H N 15	СН	N
446	N N N N N N N N N N N N N N N N N N N	СН	N
447	F ₃ CO N ⁵ , OCF ₃	СН	СН
448	H ₃ C N NH Y	СН	СН
449	O NH. X	СН	СН
450	S-N-X	СН	СН
451	S-N-X-NH-X	СН	СН
452	N= S-N NHX	СН	СН
453	MeO H F ₃ C NH	NH ₂	

Cpd	W	Υ	Z
454	MeO H N NH	NH ₂	
455	O NH Y'	СН	СН
456	MeHN—S NH \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	СН	СН
457	MeO H ₂ N H ₂ N H ₂ N	>	
458	MeO NH 1;	СН	СН
459	0, 0 NH, 1(H ₃ C	СН	CH
460	NH NH ZY	СН	N
461	H ₃ C _N NH ₂ C _{H₃}	СН	СН

Cpd	W	Υ	Z
462	HN TH	ĊH	СН
463	ОН	N	СН
464	H ₃ C S ^X	N	СН
465	HN	СН	СН
466	N HN S	СН	СН
467	Br S NH	СН	СН
468	HN-N	СН	СН

129. A compound selected from the group consisting of the following and their pharmaceutically acceptable salts:

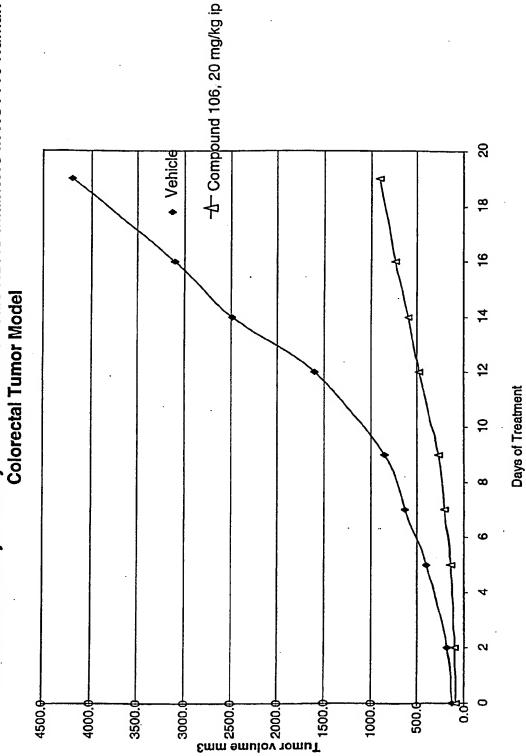
H ₂ N H ₃ C Si HN	HC NH ₂
CI H ₂ N HN	
CH ₃ S NH O H ₂ N	H ₃ C _O S H ₂ N H ₂ N
O H NH2	N NH2
NH CI N NO-CH ₃	H ₃ C O N H ₂
HN-	NH2 S H NH2
S NH ₂	S N N NH ₂
H ₃ C N NH ₂	NH ₂

H NH ₂	N NH2
NH ₂	H ₃ C NH ₂
HN H2	NH ₂
H ₃ C — N N N NH ₂	CH ₃ N CH ₃
NC — S H NH2 H-N CH3	H_3C N
OH NH2	H ₃ C O CH ₃
CH ₃ O CH ₃ O H ₂ N H ₃ C	O H ₃ C O H ₃ C
MeO H OH OH	H ₃ C-O N N NH ₂

H ₃ C-O N N NH ₂	MeO N S N HO
MeO S S	SMe HN O N HN N N H
NH NH ₂	MeO NH O HN S
MeO H OH OH OH	MeO OMe
ON H ₂ N H ₂ N S	MeO H NH ₂
H_3C N	H ₃ C NH ₂

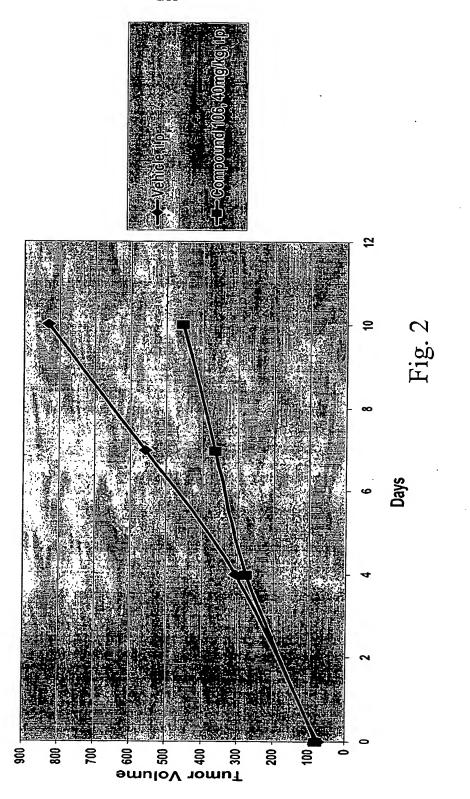
- 130. A histone deacetylase inhibitor selected from the compounds listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f, or a pharmaceutically acceptable salt thereof.
- 131. A composition comprising a compound according to any one of claim 1-130 and a pharmaceutically acceptable carrier.
- 132. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a compound according to any one of claim 1-130.

Antitumor Activity of MethylGene Small Molecule HDAC Inhibitors in HCT116 Human

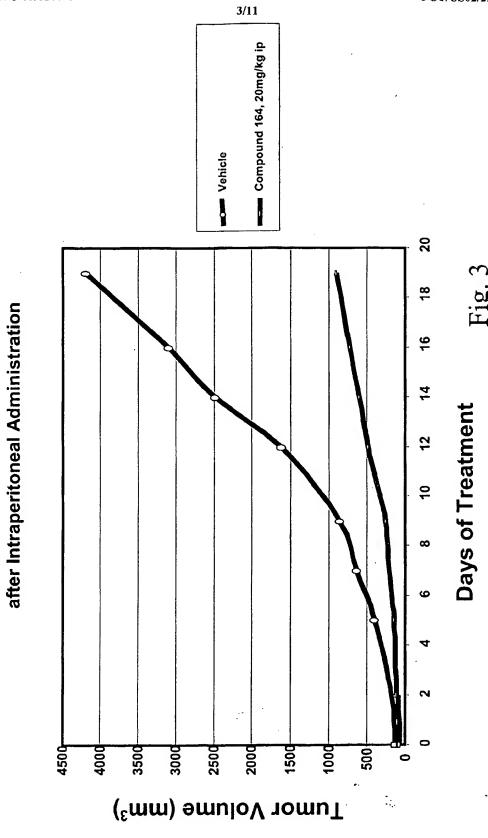


BEST AVAILABLE COPY

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 106 After Intraperitoneal Administration



Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 164



BEST AVAILABLE COPY

16

9

Days

BEST AVAILABLE COPY

■ Compound 228, 60mg/kg, P.O. Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 228 After Oral Administration Vehicle \boxtimes 1800 1600 1400 1200 1000 800 900 200 **Inmor Volume (mm3)**

4/11

8

Days

BEST AVAILABLE COPY

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 311 after Intraperitoneal Administration 1200 8 8

Tumor Volume (mm³)

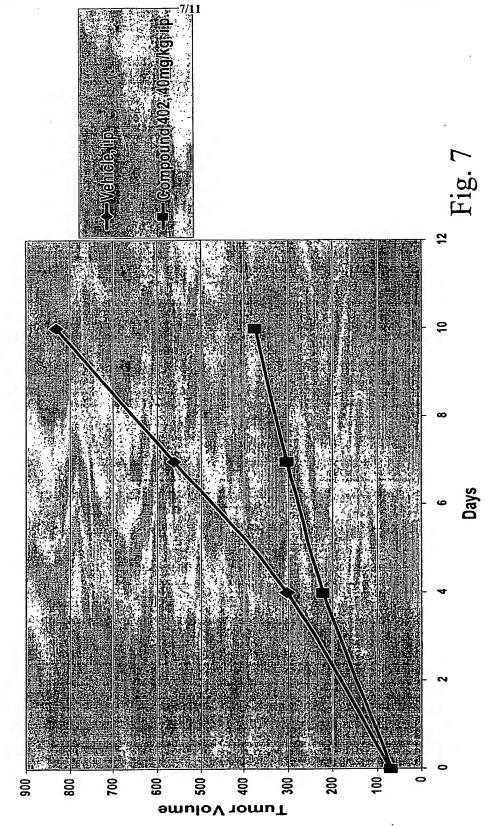
5/11

BEST AVAILABLE COPY

-Compound 376, 60mg/kg, p.o. Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 376 After Oral Administration ▼ Vehicle 12 9 Days Tumor Volume (mm³) 1800 1600 200 0

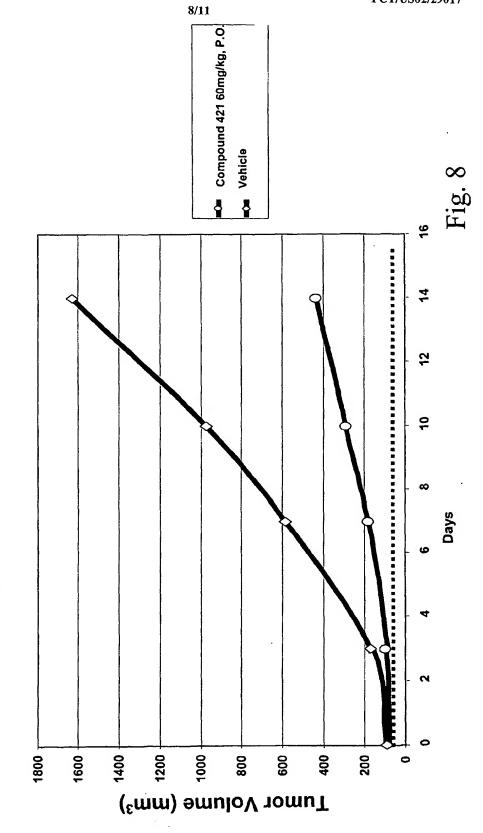
6/11

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 402 After Intraperitoneal Administration

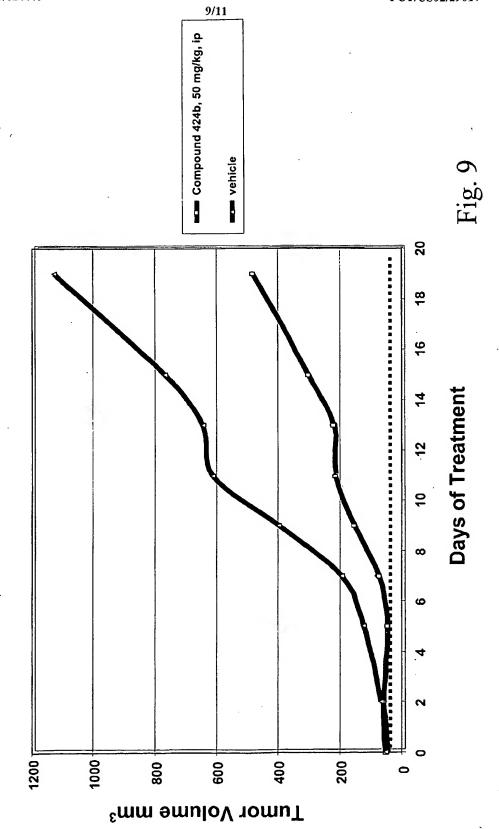


BEST AVAILABLE COPY

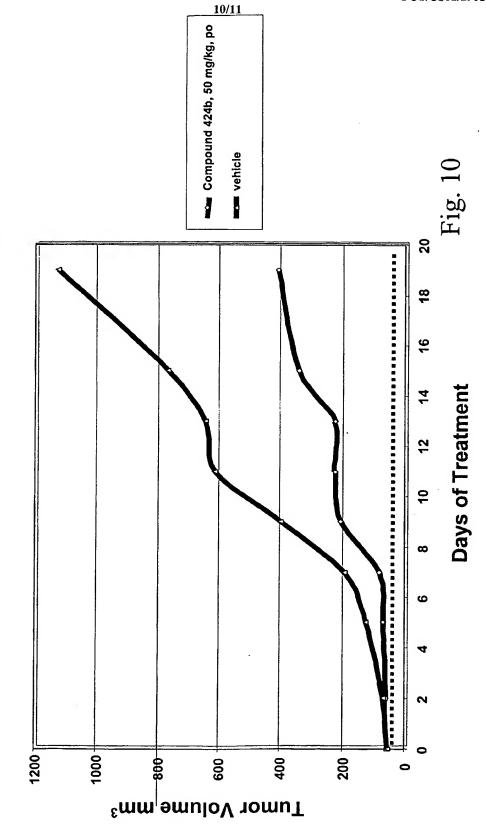
Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 421 After Oral Administration



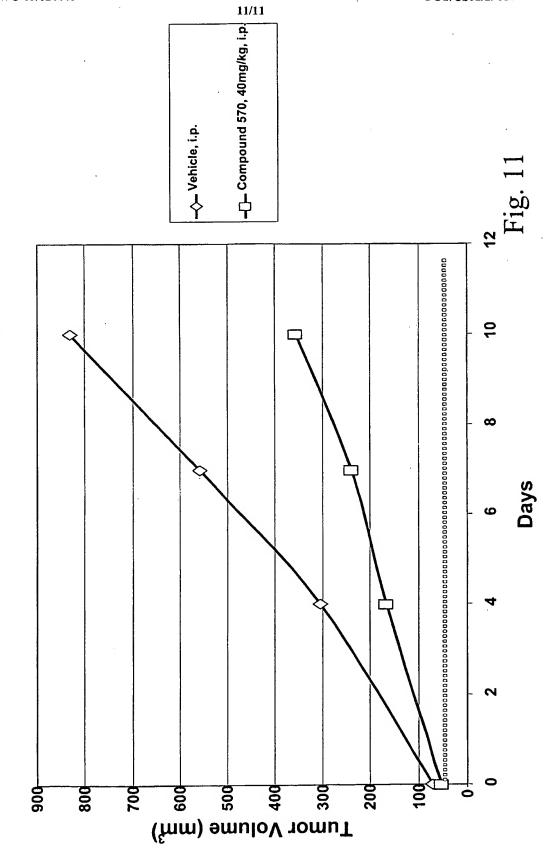
Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Intraperitoneal Administration



Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Oral Administration



Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 570 after Intraperitoneal Administration



	G.				
÷				ė	
			,		

(19) World Intellectual Property Organization International Bureau





(43) International Publication Date 27 March 2003 (27.03.2003)

(10) International Publication Number WO 03/024448 A3

- (51) International Patent Classification7: A61K 31/44. 31/506, 31/16, 31/472, 31/47, 31/428, 31/41, C07D 213/74, 401/12, 405/12, 213/82, C07C 237/20, C07D 215/38, 215/36, 239/42, 239/52, 217/04, 277/82, 277/42, 257/04, A61P 35/00
- (21) International Application Number: PCT/US02/29017
- (22) International Filing Date:

12 September 2002 (12.09.2002)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/322,402

US 14 September 2001 (14.09.2001) 26 June 2002 (26.06.2002)

- 60/391,728 (71) Applicant (for all designated States except US):
- METHYLGENE, INC. [CA/CA]; 7220 Frederick-Banting, St. Laurent, Quebec H4S 2A1 (CA).
- (72) Inventors: and
- (75) Inventors/Applicants (for US only): DELORME, Daniel [CA/CA]; 793 Charbonneau, St-Lazare, Quebec J7T 2B2 (CA). WOO, Soon, Hyung [KR/US]; 1161 Nimitz Lane, Foster City, CA 94404 (US). VAISBURG, Arkadii [CA/CA]; 10 Riverwood Grove, Kirkland, Quebec H9J 2X2 (CA). MORADEL, Oscar [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). LEIT, Silvana [AR/CA]; 27 Rolland-Laniel, Kirkland, Quebec H9J 4A5 (CA). RAEPPEL, Stephane [FR/CA]; 5041 Laurin, Pierrefonds, Quebec H8Y 3R4 (CA). FRECHETTE, Sylvie [CA/CA]; 2380 Duff Court apt.#8, Lachine, Quebec H8S 1G2 (CA). BOUCHAIN, Giliane

[FR/CA]; 247 Glengary Avenue, Beaconsfield, Quebec H9W 5X9 (CA).

- (74) Agent: GREENFIELD, Michael, S.; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Suite 3200, Chicago, IL 60606 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

of inventorship (Rule 4.17(iv)) for US only

Published:

with international search report

(88) Date of publication of the international search report: 13 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds e.g. (1) and methods for inhibiting deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. (formula 1). All definitions are as the application.

ional Application No

	INTERNATIONAL SEARCH REPO	N	PCT/US 02	/29017		
A. CLASSI IPC 7	FICATION OF SUBJECT MATTER A61K31/44 A61K31/506 A61K31/ A61K31/428 A61K31/41 C07D213 C07D213/82 C07C237/20 C07D215	/74 CO7D401	/12 CO7D			
According to	o International Patent Classification (IPC) or to both national classific			-		
	SEARCHED					
Minimum do IPC 7	commentation searched (classification system followed by classification CO7D CO7C	ion symbols)				
Documentat	ion searched other than minimum documentation to the extent that	such documents are incl	uded in the fields se	earched		
	ata base consulted during the international search (name of data be ternal, WPI Data, PAJ, BEILSTEIN Da		`)		
C. DOCUME	ENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the re	levant passages		Relevant to claim No.		
X	WO 01 38322 A (METHYLGENE INC) 31 May 2001 (2001-05-31) See compounds of the third invenwhich X1 is -L2-M2-L2- page 118; claim 1; example 31	tion in	٠.	54-132		
X	EP 0 847 992 A (MITSUI CHEMICALS 17 June 1998 (1998-06-17) See compounds in Table 1 where X than carbonyl. Directly relevant novelty of the third and fourth inventions. claim 1; table 1	is other		54-132		
Α	WO 01 16106 A (SCHERING AG ;ANDO (JP); SAKABE MASAHIRO (JP); SAKABE MASAHIRO (JP); SAKABE MASAHIRO (JP); SAKABE MARCH 2001 (2001-03-08) claim 1			1-132		
X Furth	er documents are listed in the continuation of box C.	X Patent family	members are listed i	n annex.		
"A" document defining the general state of the art which is not considered to be of particular relevance tiling date "E" earlier document but published on or after the international filing date are document with the publication but cited to understand the principle or theory underlying the invention "E" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention cannot be considered novel or cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "E" document published prior to the international filing date but later than the priority date and not in conflict with the application but cited to understand the principle or theory underlying the or priority date and not in conflict with the application but cited to understand the priority date and not in conflict with the application but cited to understand the priority date and not in conflict with the application but cited to understand the principle or theory underlying the cited to understand the principle or theory underlying the or priority date and not in conflict with the application but cited to understand the principle or theory underlying the cited to understand the principle or theory underlying the cited to understand the principle or theory underlying the cited to understand the principle or theory underlying the cited to understand the pri						
Date of the a	Date of the actual completion of the international search Date of mailing of the international search					
3 February 2003 2 0. 02.03						
Name and m	ailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	, M				

In ponal Application No PCT/US 02/29017

A. CLASSII IPC 7	CO7D239/52 CO7D217/04 CO7D277/ A61P35/00	82 CO7D277/42	C07D257/04				
According to	According to International Patent Classification (IPC) or to both national classification and IPC						
	SEARCHED						
Minimum do	cumentation searched (classification system followed by classification	n symbols)					
Documental	ion searched other than minimum documentation to the extent that sa	uch documents are included in the	e fields searched				
Electronic da	ata base consulted during the international search (name of data base	e and, where practical, search te	rms used)				
,		w.					
C. DOCUME	NTS CONSIDERED TO BE RELEVANT						
Category *	Citation of document, with indication, where appropriate, of the rela	evant passages	Relevant to claim No.				
A	SUZUKI ET AL: "Synthesis and His Deacetylase Inhibitory Activity o Benzamide Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, A	f New	1-93				
	CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 15, 1999, pages 3001-3003, XP002158227 ISSN: 0022-2623 Trichostatin A on page 3001						
E	page 3002; table 1 WO 02 069947 A (METHYLGENE INC)		54-132				
ı	12 September 2002 (2002-09-12) Claim 12 (g)-(j). Relevant for thinvention.	e second	0. 202				
		/					
		,					
ı							
X Furti	ner documents are listed in the continuation of box C.	X Patent family members	are listed in annex.				
° Special ca	legaries of cited documents :	"T" later document published after	r the international filing date				
"A" docume consid	int defining the general state of the art which is not ered to be of particular relevance	or priority date and not in co cited to understand the princ invention	nflict with the application but tiple or theory underlying the				
	"E" earlier document but published on or after the international filing date "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to						
	"L" document which may throw doubts on priority claim(s) or involve an inventive step when the document is taken alone						
which is cried to establish the publication date of another citation or other special reason (as specified) "O" document reterring to an oral disclosure, use, exhibition or comment is combined with one or more other such document.							
other means ments, such combination being obvious to a person skilled in the art.							
	an the priority date claimed	*&* document member of the san Date of mailing of the interna					
_	3 February 2003 2 6. 62.03						
	nailing address of the ISA	Authorized officer	<u> </u>				
	European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk						
	NL - 2200 TV HISWIR Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M					

In popul Application No PC1/US 02/29017

		PCT/US 02/29017						
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT								
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
P,X	US 2002/061860 A1 (LI, ZUOMEI ET AL) 23 May 2002 (2002-05-23) Compound 3. Second invention page 7	54-132						
X	WO 00 03704 A (SMITHKLINE BEECHAM CORP; FRANZ ROBERT G (US); WEINSTOCK JOSEPH (US) 27 January 2000 (2000-01-27) Third and fourth inventions. claim 1; examples 1,2	54						
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; N,N'-di(o-aminophenyl)terephthalamide, Database accession no. 5619310 XP002229372 Third invention. abstract & INDIAN J. CHEM. SECT. B., vol. 25, 1986, pages 1146-1149,	54						
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3016237 XP002229373 4,6-dimino-N,N'-bis-(2-amino-phenyl)-isoph thalamide. Third invention. abstract & CHEM. HETEROCYCL. COMPD., vol. 13, 1977, pages 1029-1032,	54						
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 3458834 XP002229374 4,6-dimino-N,N'-bis-(2-amino-phenyl)-phtha lamide. Third invention. abstract & JUSTUS LIEBIGS ANN. CHEM., vol. 347, 1906, page 116 -/	54						

In post Application No PCT/US 02/29017

		PC1/US 02/29017		
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to daim No.	
x	PICARD ET AL: "Desymmetrization Reactions: A Convenient Syntheseis of Aromatic Diamide Diamines" SYNTHESIS, vol. 10, 2001, pages 1471-1478, XP001097260 See compounds 3i, 3j, 3k, 3q and 3t. Third invention. page 1472; table 2	·	54	
X	RABILLOUD G ET AL: "Réactions de condensation de l'o-phénylènediamine avec les benzoxazin-3,1-ones-4 substituées en position 2" BULL. SOC. CHIM. FR., 1975, pages 2682-2686, XP009005073 page 2682; example 4C		54	
			·	
			,	

national application No. PCT/US 02/29017

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of Iirst sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 132 is are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. X Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. X No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 54-129 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search for the compounds 2 as defined in claim 54 has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the (2) claim 54 where X1 is not a covalent bond and where Ay2 is either (substituted) phenyl or (substituted) thiophene. This appears to cover all of the examples and all of the specifically preferred forms.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-53 and claim 130 (part)

(1) and (1a)

2. Claims: 54 (part), 55 (part), 57-59 (all part), 61-63 (all part),64-67,68-82 (part),83-89, 90-93 (part), 129-132 (all part)

compounds (2) and (3) where q=1

3. Claims: 54 (part), 55 (part), 56,57-59 (all part),60, 61-63 (all part),68-82 (all part), 90-93 (all part) 94-128, 129-132 (all part):

compounds (2) and (3) which have an NH2-oBe-N-C(0)- group and q=0.

4. Claims: claims 54 (part), 57-59 (all part), 61-63 (all part) 129-132 (all part):

compounds (2) and (3) where Ay2 is not ortho aniline (e.g. it is thiophene in 4 of the last 7 compounds on page 335) and q=0.

Ir ___onal Application No PCT/US 02/29017

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0138322	Α	31-05-2001	AU EP WO	1876801 A 1233958 A 0138322 A	١1	04-06-2001 28-08-2002 31-05-2001
EP 0847992	Α	17-06-1998	EP JP JP US	0847992 A 10152462 A 2002332267 A 6174905 B	l	17-06-1998 09-06-1998 22-11-2002 16-01-2001
WO 0116106	A	08-03-2001	JP AU BG BR CN CZ WO EP NO SK	2001081031 A 6841600 A 106439 A 0013648 A 1371366 T 20020724 A 0116106 A 1208086 A 20020952 A	N N N N N N N N	27-03-2001 26-03-2001 29-11-2002 07-05-2002 25-09-2002 17-07-2002 08-03-2001 29-05-2002 20-03-2002 10-09-2002
WO 02069947	Α	12-09-2002	WO US	02069947 A 2002137162 A		12-09-2002 26-09-2002
US 2002061860	A1	23-05-2002	WO US	03006652 A 2002137162 A		23-01-2003 26-09-2002
WO 0003704	Α	27-01-2000	CA EP WO	2338122 A 21100484 A 0003704 A	۱1	27-01-2000 23-05-2001 27-01-2000

THIS PAGE BLANK (USPTO)